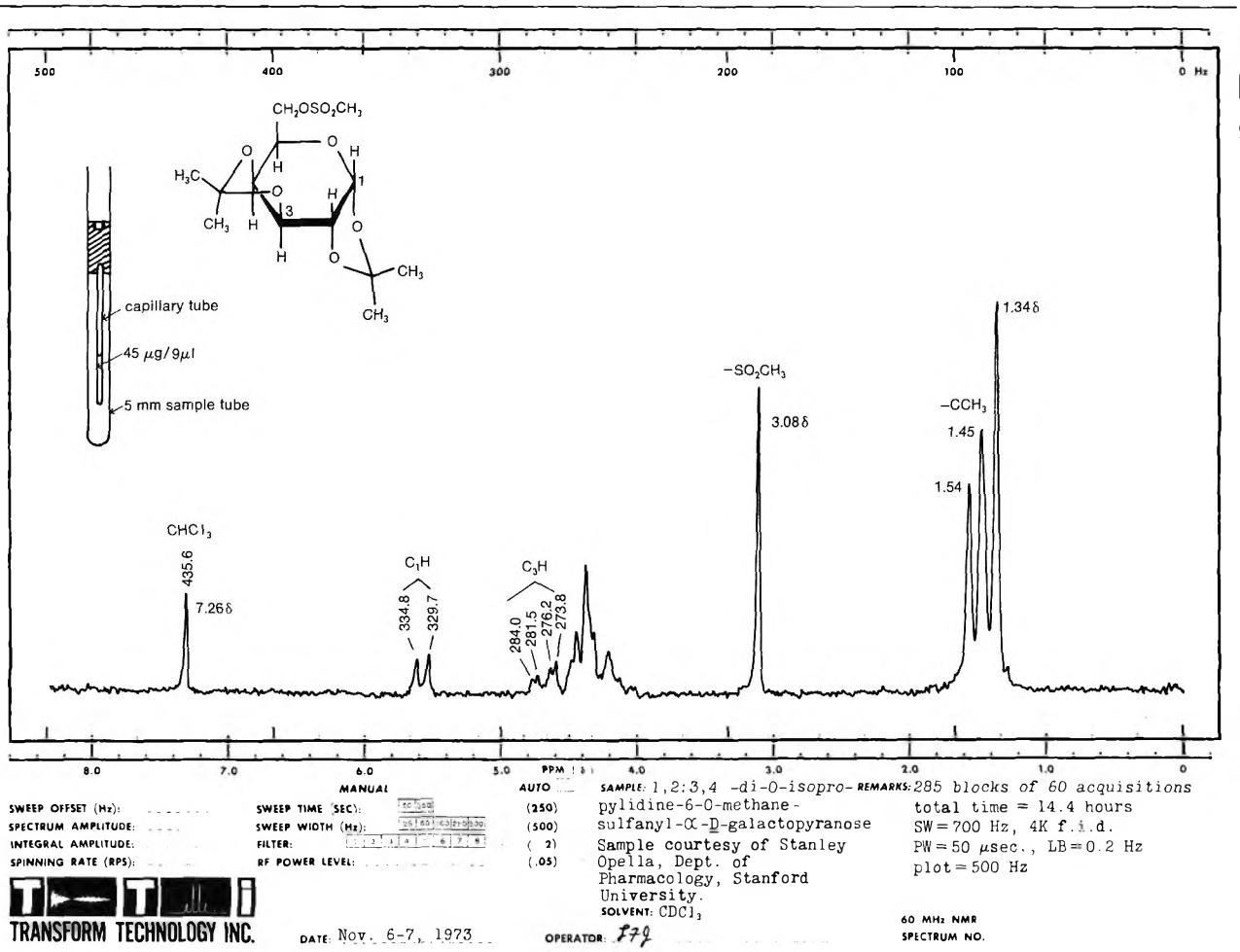
VOLUME 39 MARCH 8, 1974 NUMBER 5 JOCEAH

THE JOURNAL OF Organic Chemistry

PUBLISHED BIWEEKLY BY THE AMERICAN CHEMICAL SOCIETY



Analysis of very small samples is best done using a microcell approach. Here, 45 micrograms of a compound with molecular weight 338 was contained in a capillary tube of 1.0 mm I.D. The peak at 3.08δ, although weak after one block of acquisitions, served adequately for the peak register method, which effectively cancels long-term field drift. Signal frequencies and chemical shifts were copied from an oscilloscope display of peak positions using an assigned value of 435.6 Hz for the chloroform peak. The spectrum is very well defined, and demonstrates that overnight FT operation with a T-60A/TT-7 system is quite feasible and very useful for microsample analysis.

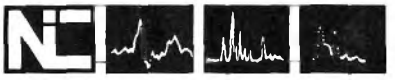
MICROSAMPLE ANALYSIS with a TT-7/T-60A System

The TT-7 pulsed RF Fourier transform accessory benefits NMR operation by dramatically increasing sensitivity over that obtained in the normal CW mode of operation. Typically, samples five to ten times smaller than those now being handled can be run in the same amount of analysis time. Signal input, accumulated free induction decay, or transformed spectra can be displayed on the TT-7's cathode ray tube for visual monitoring. The spectra can be plotted using the T-60 recorder. Digital integrations of spectra can be viewed or plotted as well.

Not only will the TT-7 enhance the sensitivity and increase sample throughput of your T-60 but it will also provide an excellent Fourier transform training facility. Its ease of use is incomparable. In addition, spin-lattice relaxation times can be determined from a series of runs using the progressive saturation technique. Optional automatic T_1 measurements are available using the inversion-recovery technique as well as other multi-pulse experiments. In addition to sensitivity improvement and T_1 measurement applications, the basic TT-7 system will provide computer calculations of theoretical NMR spectra of up to six spins (seven spins with 12K core memory and disk memory system).

Phone or write for more details.

NICOLET INSTRUMENT CORPORATION



5225 Verona Road, Madison, Wisconsin 53711
Phone: 608/271-3333

THE JOURNAL OF Organic Chemistry

Published by the
AMERICAN CHEMICAL SOCIETY
1155 16th Street, N.W.
Washington, D. C. 20036

BOOKS AND JOURNALS DIVISION

John K Crum *Director*

Ruth Reynard *Assistant to the Director*

Charles R. Bertsch *Head, Editorial Processing Department*

D. H. Michael Bowen *Head, Journals Department*

Bacil Guiley *Head, Graphics and Production Department*

Seldon W. Terrant *Head, Research and Development Department*

Published biweekly by the American Chemical Society at 20th and Northampton Sts., Easton, Pa. 18042. Second-class postage paid at Washington, D. C., and at additional mailing offices.

Editorial Processing Department, American Chemical Society, 20th and Northampton Sts., Easton, Pa. 18042: Head, Charles R. Bertsch; Production Editor, Eileen B. Segal; Assistant Editor, Fern S. Jackson; Editorial Assistant, Andrew J. D'Amelio.

Advertising Office: Centcom, Ltd., 142 East Ave., Norwalk, Conn. 06851.

The American Chemical Society and the Editors of *The Journal of Organic Chemistry* assume no responsibility for the statements and opinions advanced by contributors.

Business and Subscription Information

Send all new and renewal subscriptions *with payment* to Office of the Controller, 1155 16th Street, N.W., Washington, D. C. 20036. Subscriptions should be renewed promptly to avoid a break in your series. All correspondence and telephone calls regarding changes of address, claims for missing issues, subscription service, the status of records, and accounts should be directed to Manager, Membership and Subscription Services, American Chemical Society, P.O. Box 3337, Columbus, Ohio 43210. Telephone (614) 421-7230.

On changes of address, include both old and new addresses with ZIP code numbers, accompanied by mailing label from a recent issue. Allow four weeks for change to become effective.

Claims for missing numbers will not be allowed (1) if loss was due to failure of notice of change in address to be received before the date specified, (2) if received more than sixty days from date of issue plus time normally required for postal delivery of journal and claim, or (3) if the reason for the claim is "issue missing from files."

Subscription rates for 1974: $20.00 per volume to members of the ACS and $60.00 per volume to all others. Those interested in becoming members should write to the Admissions Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Add $5.00 per subscription for Canada and countries belonging to the Postal Union, and $6.00 for all other countries.

Single copies for current year: $3.00. Postage, single copies: to Canada and countries in the Pan-American Union, $0.15; all other countries, $0.20. Air freight rates available on request. Rates for back issues from Volume 20 to date are available from the Special Issues Sales Department, 1155 16th St., N.W., Washington, D. C. 20036.

Subscriptions to this and the other ACS periodical publications are available on microfilm. Supplementary material not printed in this journal is now available in microfiche form on a current subscription basis. For information on microfilm or microfiche subscriptions, write Special Issues Sales Department at the address above.

Notice to Authors last printed in the issue of June 1, 1973

JOCEAH 39 (5) 587-758 (1974)
ISSN 0022-3263

THE JOURNAL OF Organic Chemistry

VOLUME 39, NUMBER 5 MARCH 8, 1974

NOTES

COMMUNICATIONS

■ Supplementary and/or miniprint material for this paper is available separately, in photocopy of microfiche form. Ordering information is given in the paper.

* In papers with more than one author, the asterisk indicates the name of the author to whom inquiries about the paper should be addressed.

AUTHOR INDEX

THE JOURNAL OF Organic Chemistry®

VOLUME 39, NUMBER 5

MARCH 8, 1974

Reaction of Pyrimidines with Diarylmethyl Cations

Calvert W. Whitehead,* Celia A. Whitesitt, and Allen R. Thompson

The Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana 46206

Received October 12, 1973

Pyrimidine is not alkylated by diarylmethyl cations, but substitutions do occur at an endocyclic nitrogen with 2- and 4-hydroxypyrimidine and at the sulfur of 2-mercaptopyrimidine. Diarylmethylations occur exclusively at the 5-carbon position of 2,4-dihydroxy-, 2,4,6-trihydroxy-, and 6-amino-2,4-dihydroxypyrimidines. The effects of Lewis acid catalysts as well as substituents on the diarylmethyl cations on the alkylation reactions are discussed. Also, alternate synthetic routes to the 5-diarylmethylpyrimidines are given.

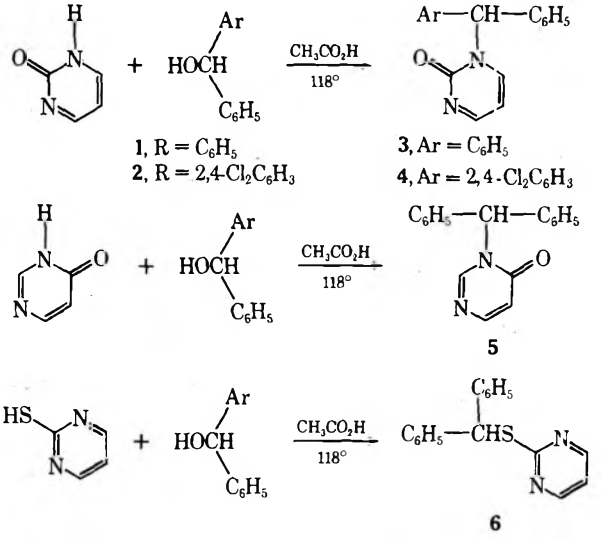
Pyrimidine and pyrimidine derivatives present several electron-rich nucleophilic centers where a carbonium ion may attack. Only one example of this reaction is reported with a diarylmethyl cation, and in this case the extranuclear nitrogen of 2-aminopyrimidine is alkylated.[1] On the other hand, alkylations of a carbon atom are reported for 2-hydroxypyridine,[2] thiophene,[3] 9-methylcarbazole,[4] pyrrole,[5] hydroxyquinolines,[6] and indoles.[7] The 2-, 4-, and 6-carbon atoms in pyrimidine are electron deficient by virtue of the electron-withdrawing effect of the nitrogen atoms and are not susceptible to alkylation.[8] Carbonium ion alkylations, therefore, could be expected to take place only at an electron-rich ring nitrogen or perhaps at the 5-carbon atom, although the latter is made slightly electron deficient by the general inductive effect. This report describes the reactions of diarylmethyl carbonium ions with pyrimidine, mercaptopyrimidine, and hydroxypyrimidines.

Results

No C or N alkylation products of pyrimidine were isolated when pyrimidine was treated with benzhydrol (1) in acetic acid either in the presence or absence of a Lewis acid catalyst. A very small amount of *N*-acetyl(diphenylmethyl)amine was isolated and the remaining 1 was recovered as diphenylmethyl acetate. The conversion of 1 to diphenylmethyl acetate was shown to occur quantitatively within 15 min in hot acetic acid.

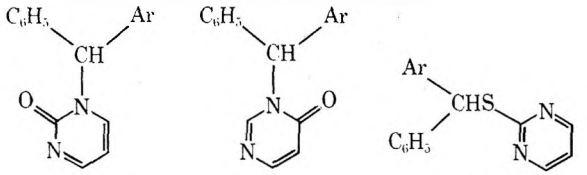
One electron-releasing substituent on pyrimidine, such as hydroxy or mercapto group in the 2 or 4 position, supplied sufficient electron density for electrophilic attack to take place at one of the heteroatoms (Scheme I). Partial alkylation of 2-hydroxypyrimidine occurred with 1 and with 2,4-dichlorobenzhydrol (2) in acetic acid to give low yields of the respective 1-diarylmethyl-2(1*H*)-pyrimidinones (3 and 4, Table I). Addition of boron trifluoride had little effect. More complete alkylation of 4-hydroxypyrimidine occurred with 1 to furnish 3-diphenylmethyl-4(3*H*)-pyrimidinone (5, Table I). The diphenylmethyl cation attacked the extranuclear sulfur of 2-mercaptopyrimidine to give a moderately good yield of [(2-diphenylmethyl)thio]pyrimidine (6, Table I).

Scheme I



Two or three electron-contributing groups at the 2, 4, and 6 positions of pyrimidine caused the diarylmethyl cations to be attracted to the 5 position of pyrimidine (Scheme II). Reaction of uracil or 2-thiouracil, however, did not occur with 1 after 5 days in refluxing acetic acid. When boron trifluoride or stannic chloride was added, the alkylation was complete in several hours and nearly quantitative yields of the 5-(diphenylmethyl) derivatives (7 and 8, Table II) were isolated. Similar reaction conditions with 1 and 6-methyluracil gave a good yield of 6-methyl-5-(diphenylmethyl)uracil (9, Table II). Chlorine substituents of 2 had only a slightly inhibitory effect on the carbonium ion alkylations of uracil and 6-methyluracil. Yields of the 5-[(2,4-dichloro)diphenylmethyl]uracils (10 and 11, Table II) were only a few per cent lower than the yields for the corresponding 5-(diphenylmethyl)uracils (7 and 8).

Table I
***N*-Diarylmethylpyrimidines and [(2-Diphenylmethyl)thio]pyrimidine**

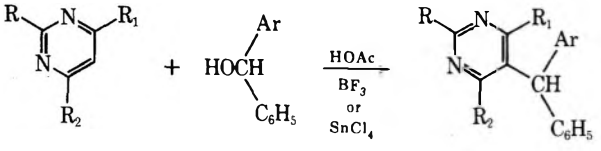


3, 4 5 6

Compd no.	Ar	Mp, °C	% yield
3	C_6H_5	204	13
4	2,4-$Cl_2C_6H_3$	185–187	18
5	C_6H_5	158–159	51
6	C_6H_5	104	63

However, the chloro substituents had a pronounced inhibitory effect upon the reactions with 4,6-dihydroxypyrimidine and 4,6-dihydroxy-2-(methylthio)pyrimidine. A 40% yield of 5-[(2,4-dichloro)diphenylmethyl]uracil (**12**, Table II) was obtained from **2** and 4,6-dihydroxypyrimidine, compared with a 78% yield of 4,6-dihydroxy-5-(diphenylmethyl)pyrimidine (**13**, Table II) obtained from **1** and 4,6-dihydroxypyrimidine. A very low yield of 5-[(2,4-dichloro)diphenylmethyl]-4,6-dihydroxy-2-(methylthio)pyrimidine (**14**, Table II) resulted from 4,6-dihydroxy-2-(methylthio)pyrimidine and **2** while the similar 4,6-dihydroxy-2-methylpyrimidine reacted quantitatively with **1** to give 4,6-dihydroxy-5-(diphenylmethyl)-2-methylpyrimidine (**15**, Table II).

Scheme II

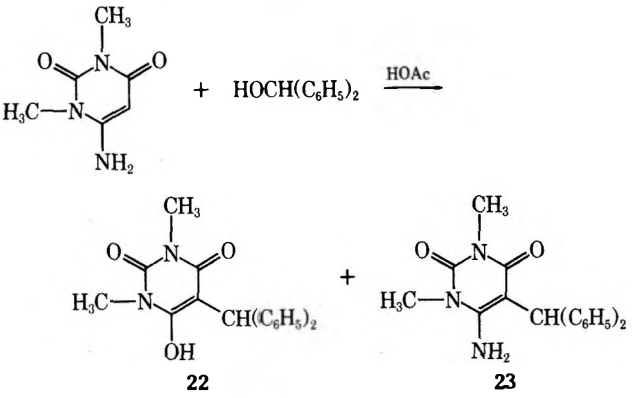


Barbituric acid was alkylated by diarylmethyl cations without the aid of strong acid catalysts, but the yields were low (Table II), even with longer than usual reaction times. When either stannic chloride or boron trifluoride was present, alkylation with **1**, 4-chlorobenzhydrol, or **2** gave good to excellent yields of the respective 5-diarylmethylbarbituric acids (**16**, **17**, and **18**). The alkoxy groups of 3,4-diethoxybenzhydrol retarded the alkylation reaction of barbituric acid (**19**, Table II), but this effect was less than that observed with the 2,4-dichloro- and 4-chlorobenzhydrols. Tritylation of barbituric acid was accomplished, but because of an unusual and interesting behavior of the product the results will be reported in another paper.

A Lewis acid catalyst did not enhance the diphenylmethylation of 6-aminouracil. The yield of 6-amino-5-(diphenylmethyl)uracil (**20**, Table II) obtained without the catalyst was twice that with the catalyst. Alkylations of hydroxypyrimidines by diphenylmethyl cation were attempted in concentrated sulfuric acid and in polyphosphoric acid; both were unsuccessful because of low yields. Sulfuric acid, added to the acetic acid solution, may have catalyzed the reaction of **1** with 4-amino-6-hydroxy-2-pyrimidinethiol to give a 52% yield of 4-amino-6-hydroxy-5-(diphenylmethyl)-2-pyrimidinethiol (**21**, Table II).

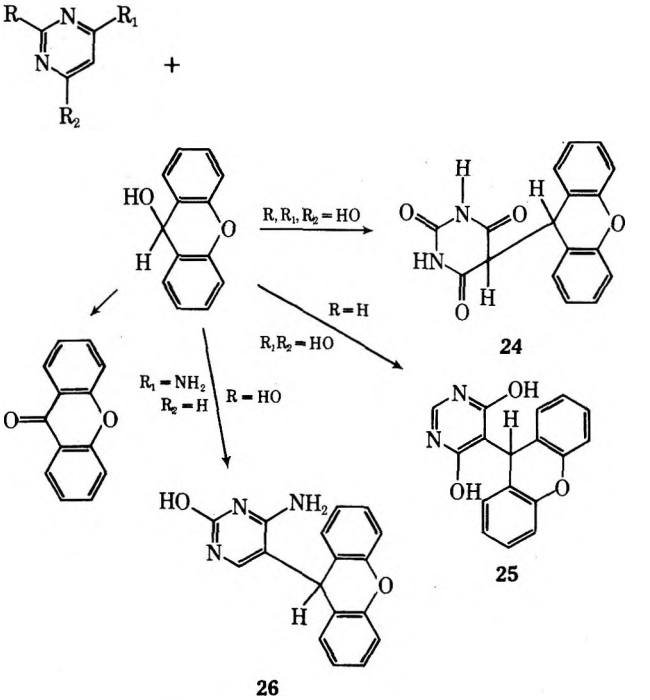
A Lewis acid catalyst was not required for the reaction between **1** and 6-amino-1,3-dimethyluracil. Alkylation at the 5-carbon position was at least 80% complete in hot acetic acid. Partial hydrolysis of the 6-amino group occurred and the reaction mixture yielded the major product 1,3-dimethyl-5-(diphenylmethyl)barbituric acid (**22**) and the minor product 6-amino-1,3-dimethyl-5-(diphenylmethyl)uracil (**23**, Scheme III).

Scheme III



Xanthen-9-ol is completely oxidized to xanthen-9-one within 15 min in hot acetic acid. Successful competitive alkylations of pyrimidines by xanthen-9-ol occurred rapidly or otherwise not at all. Barbituric acid and 4,6-dihydroxypyrimidine gave excellent yields of the corresponding 5-(9-xanthenyl)pyrimidines (**24** and **25**, Table III). Attempted reactions with uracil and thiouracil, on the other hand, failed because of their low solubility in acetic acid. Cytosine gave a 55% yield of 5-(9-xanthenyl)cytosine (**26**, Table III), but only a very low yield of 4-amino-5-(diphenylmethyl)-2-hydroxypyrimidine (**27**, Table II) was obtained from cytosine and **1**.

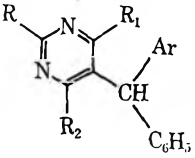
Scheme IV



26

Since fluoren-9-ol was oxidized in acetic acid, reactions of this tricyclic carbinol with hydroxypyrimidines were not attempted. The reaction of 10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5-ol with uracil gave a moderately good yield of 5-(10,11-dihydro-5*H*-dibenzo[*a*,*d*] cyclohepten-5-yl)uracil (**28**, Table III) and with barbituric acid gave an excellent yield of 5-(10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5-yl)barbituric acid (**29**, Table III). The large dibenzo[*a*,*d*]cycloheptene group of **29** is restricted from freely rotating about the bond to the pyrimidine ring. The nmr doublet signal, centered at 3.85 ppm from the pyrimidyl-5 proton, and the doublet, centered at 4.50

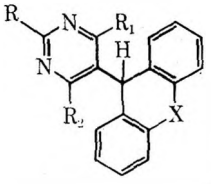
Table II
5-Diarylmethylhydroxypyrimidines and 5-Diarylmethyl Mercaptopyrimidines



No.	R	R_1	R_2	Ar	Mp, °C	% yield
7	HO	HO	H	C_6H_5	298–300	96[a]
8	HS	HO	H	C_6H_5	264	99
9	HO	HO	CH_3	C_6H_5	285–287	80[b]
10	HO	HO	H	2,4-$Cl_2C_6H_3$	294	81,[a] 95[c]
11	HO	HO	CH_3	2,4-$Cl_2C_6H_3$	247–249	71[b]
12	H	HO	HO	2,4-$Cl_2C_6H_3$	305	40
13	H	HO	HO	C_6H_5	329–330	78
14	CH_3S	HO	HO	2,4-$Cl_2C_6H_3$	255	14
15	CH_3	HO	HO	C_6H_5	>300	98
16	HO	HO	HO	C_6H_5	220	98[b,c]
17	HO	HO	HO	4-ClC_6H_4	110[d]	73[e]
18	HO	HO	HO	2,4-$Cl_2C_6H_3$	234	67,[a,f] 83[b]
19	HO	HO	HO	3,4-$(C_2H_5O)_2C_6H_3$	180–182	42
20	HO	HO	NH_2	C_6H_5	330–342	67[g]
21	HS	NH_2	OH	C_6H_5	170–180[d]	52
27	HO	NH_2	H	C_6H_5	236	4[h]

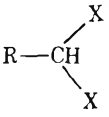
[a] $SnCl_4$ was used as catalyst (5 g/0.1 mol). [b] With BF_3 catalyst (5 g/0.1 mol). [c] The yield was 56% without BF_3 catalyst. [d] Solvated. [e] The yield was 37.5% without BF_3. [f] The yield was 22% without catalyst. [g] The yield was 38.5% with $SnCl_4$ catalyst. [h] The same reaction conditions were used for compound **21**.

Table III
5-(9-Xanthenyl)- and 5-(10,11-Dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5-yl)pyrimidines



Compd no.	X	R	R_1	R_2	Mp, °C	% yield
24	O	HO	HO	HO	290	81
25	O	H	HO	HO	285	95
26	O	HO	H_2N	H	320 dec	55
28	$(CH_2)_2$	HO	HO	H	295	68
29	$(CH_2)_2$	HO	HO	HO	244–246	85

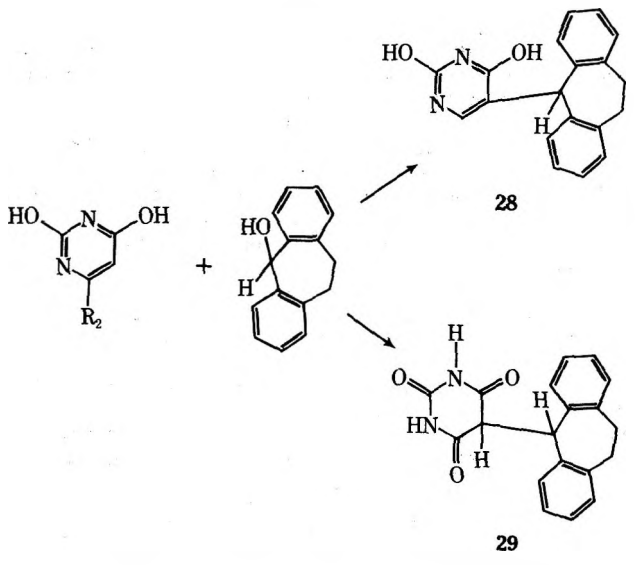
Table IV
Aralkyl Malononitriles and Malondiamides



Compd no.	R	X	Mp, °C	% yield
30	$(C_6H_5)_2CH$	$CONH_2$	285	91.2
31	2,4-$Cl_2C_6H_3CHC_6H_5$	$CONH_2$	270–274	55.6[a]
32	$(C_6H_5)_2CH$	C≡N	62–64	87
33	2,4-$Cl_2C_6H_3CHC_6H_5$	C≡N	108–114	85
34	$C_{13}H_9O$[b]	C≡N	184	75
35	$(C_6H_5)_3C$	C≡N	155	45.5

[a] The yield was reduced to 47.4% when glacial acetic acid was used as the reaction solvent. [b] Xanthen-9-yl.

Scheme V



ppm from the 9,10-dihydrobenzo[*a*,*d*]cycloheptenyl-5 proton, have *J* values of 9 Hz indicating that the molecule exists approximately two-thirds of the time in the trans configuration. Rotation of the xanthen-9-ol group bonded to the 5 position of barbituric acid, as in **25**, is not restricted and the signals from the vicinal protons at the bond are split by only 3 Hz.

An alternate synthesis of 5-diarylmethylpyrimidines was investigated wherein malonic acid derivatives were alkylated by arylmethyl cations, and the products were cyclized. Malononitrile failed to react with either **1** or **2** in hot acetic acid and, when boron trifluoride was added, exothermic reactions occurred to give intractable mixtures of products. However, the two carbinols did react with malondiamide in acetic acid and boron trifluoride (Scheme VI) but gave low yields of the diarylmethylmalondiamides (**30** and **31**, Table IV). Yields improved when the solvent was formic acid and a nearly quantitative yield of diphenylmethylmalondiamide (**30**) was obtained. The halogen substituents of **2**, here again, retarded the carbonium ion reaction and a lower yield of 2,4-dichloro(diphenylmethyl)malondiamide (**31**) resulted. The malondiamides (**30** and **31**) were dehydrated with phosphorus oxychloride in acetamide to give good yields of the corresponding diarylmethylmalononitriles (**32** and **33**, Table IV). The reactions of xanthen-9-ol and triphenyl-

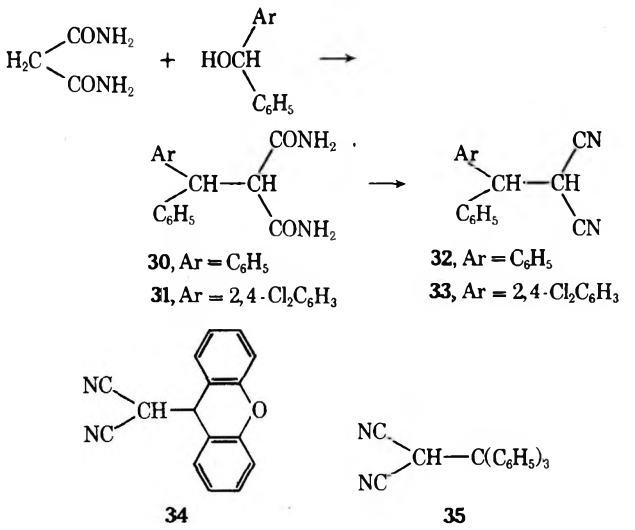
Table V
Cyclizations of 2-Diarylmethylmalondiamides (Compounds 12 and 13)

Base	$HCONH_2$, ml	$(CH_3)_2SO$, ml	Temp, °C	Time, hr	% yield of pyrimidine	% recovery of diamide
$KOC(CH_3)_3$	150	0	Reflux	3	<2[a]	*ca.* 90
$NaOC_2H_5$	50	d	Reflux	10	0[a]	*ca.* 100
$KOC(CH_3)_3$	50	50	100	15	46.8[a]	26
$NaOCH_3$	50	50	100	15	38.8[a]	52
$NaOCH_3$	40	60	135	16	53.2[a]	25
$NaOCH_3$[b]	50	50	125	15	78[a]	17
$NaOCH_3$	50	50	125	15	60.5[c]	25
NaOH	50	50	125	7	8.6[c]	75

[a] Results for 4,6-dihydroxy-5-(diphenylmethyl)pyrimidine. [b] After the initial addition of 2.2 equiv (6 g) of $NaOCH_3$, 2 g was added at 2- and 4-hr intervals. [c] Results for 5-[(2,4-dichloro)diphenylmethyl]-4,6-dihydroxypyrimidine.

methanol with malononitrile in acetic acid were uncomplicated and gave good yields of the arylmethylmalononitriles (**34** and **35**, Table IV).

Scheme VI

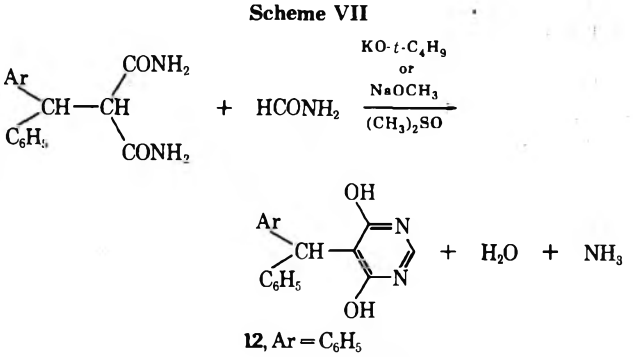


30, Ar = C_6H_5
31, Ar = 2,4-$Cl_2C_6H_3$
32, Ar = C_6H_5
33, Ar = 2,4-$Cl_2C_6H_3$

34 **35**

The malondiamides (**30** and **31**) failed to cyclize when heated neat with formamide, with formamide in formic acid, or with formamide and formic acid in dimethylformamide. Cyclization also failed with formamide in acetic acid, in sulfuric acid, or in polyphosphoric acid. Only small yields of the desired pyrimidines (**12** and **13**, Table V) were obtained when formamide was heated with **30** and **31** in alcohol in the presence of sodium methylate. The most complete cyclizations (Scheme VII) were accomplished in dimethyl sulfoxide solution with formamide and 2.2 mol equiv or more of either potassium *tert*-butoxide or sodium methoxide (Table V).

Scheme VII



12, Ar = C_6H_5
13, Ar = 2,4-$Cl_2C_6H_3$

The 5-diarylmethyluracils **10** and **7** were converted to the corresponding 2,4-dichloropyrimidines and the halogens on the pyrimidine ring were selectively and quantitatively removed by catalytic reduction[9] to give 5-diarylmethylpyrimidines.

Experimental[10] Section

1-Diarylmethyl-2(1*H*)-pyrimidones (3 and 4), 3-(Diphenylmethyl)-4(3*H*)-pyrimidinone (5), and 2-[(Diphenylmethyl)thio]pyrimidine (6) (Table I). 2-Hydroxy-, 4-hydroxy-, and 2-thiopyrimidines (0.1 mol) were heated separately with 0.1 mol of the appropriate diarylcarbinol in 50–100 ml of glacial acetic acid for 5–8 hr in the absence of a catalyst. The solid products, obtained by pouring the cooled solution into water, were crystallized from mixtures of benzene–petroleum ether, ethyl acetate–petroleum ether, and dilute alcohol.

This same procedure was repeated with 2-hydroxypyrimidine and benzhydrol with 5.0 g of boron trifluoride etherate. The yield was increased by 2%.

5-Diarylmethyluracils (7–11) (Table II). Uracil, 2-thiouracil, or 6-methyluracil (0.1 to 0.80 mol) and an equal molar quantity of the appropriate diarylcarbinol were added to glacial acetic acid (100 ml for each 0.1 mol of the uracil). Five grams of boron trifluoride etherate or 3–5 g of $SnCl_4$ was added for each 0.1 mol of the uracil. The mixture was heated at refluxing temperature until the reaction was complete, usually about 5 hr. The reaction end point was determined by periodically withdrawing and inspecting samples. The product precipitated and crystallized when a sample of a completed reaction solution was added to cold water. Oily mixtures, containing some diarylcarbinol acetate, were obtained from incomplete reaction mixtures. The completed reaction solution was cooled and poured into cold water. The solid product was collected by filtration, washed several times with water, and crystallized from alcohol–water mixtures.

The above procedure was repeated with uracil, with the exception that diphenylmethyl bromide was substituted for the diarylcarbinol. The yield of compound **7** was 74%.

5-Diarylmethyl-4,6-dihydroxypyrimidines (12–15) (Table II). 4,6-Dihydroxypyrimidine, 4,6-dihydroxy-2-(methylthio)pyrimidine, or 4,6-dihydroxy-2-methylpyrimidine (0.1 mol) and benzhydrol or 2,4-dichlorobenzhydrol (0.1 mol) were added to 100 ml of glacial acetic acid. $SnCl_4$ (2–6 g) was added and the mixture was heated at refluxing temperature for 4–5 hr. The cooled reaction mixtures were poured into cold water. The precipitated products were collected and crystallized from alcohol.

5-Diarylmethylbarbituric Acids (16–19) (Table II). Barbituric acid (12.7 g or 0.1 mol) and the appropriate diarylcarbinol (0.1 mol), boron trifluoride etherate (5 g) or $SnCl_4$ (3 g), in 100–200 ml of glacial acetic acid were heated at refluxing temperature for 2–5 hr. The reaction time was 2–5 days when the Lewis acid catalyst was not used. The products were isolated and purified in the manner described in the previous paragraph.

6-Amino-5-(diphenylmethyl)uracil (20) (Table II). Two mixtures were prepared, consisting of 0.1 mol (12.7 g) of 6-aminouracil and 0.1 mol (18.4 g) of benzhydrol in 100 ml of glacial acetic acid. Four grams of $SnCl_4$ was added to one mixture. Each mixture was heated at refluxing temperature for 24 hr. The product was isolated in the manner described in a previous paragraph.

4-Amino-5-(diphenylmethyl)-6-hydroxy-2-pyrimidinethiol (21) (Table II). Benzhydrol (19.8 g or 0.1 mol), 4-amino-6-hydroxy-2-pyrimidinethiol (14.2 g of 0.1 mol), and 1 ml of concentrated H_2SO_4 were added to 100 ml of glacial acetic acid. The mixture was heated at refluxing temperature for 6 hr, then cooled and added to water. The product was collected and crystallized from benzene, ethyl acetate, and alcohol.

5-Diphenylmethyl-1,3-dimethylbarbituric Acid and 6-

Amino-5-(diphenylmethyl)-1,3-dimethyluracil (22 and 23). 6-Amino-1,3-dimethyluracil (15.5 g or 0.1 mol) and benzhydrol (19.8 g or 0.1 mol) were heated under reflux for 6 hr in 100 ml of glacial acetic acid. The cooled solution was added to water. The precipitated solid was collected and was crystallized from methanol to yield 20 g or 65% of 5-(diphenylmethyl)-1,3-dimethylbarbituric acid (22), mp 167–168°.

Anal. Calcd for $C_{19}H_{18}N_2O_3$: C, 70.79; H, 5.63; N, 8.69. Found: C, 70.73; H, 5.77; N, 8.82.

The methanol filtrate from the above crystallization was concentrated to give 6-amino-5-(diphenylmethyl)-1,3-dimethyluracil (23) that melted at 225° after several recrystallizations, yield 5 g or 15.5%.

Anal. Calcd for $C_{19}H_{19}N_3O_2$: C, 71.01; H, 5.96; N, 13.08. Found: C, 71.08; H, 5.93; N, 12.87.

5-(Xanthen-9-yl)- and 5-(10,11-Dihydro-5*H*-dibenzo[*a,d*]cyclohepten-5-yl)pyrimidines (24, 26, 28, 29) (Table III). To 0.1 mol of barbituric acid, 4,6-dihydroxypyrimidine, or cytosine in 200 ml of glacial acetic acid was added 0.1 mol of xanthen-9-ol. A dark blue color developed almost immediately upon heating and appeared to become less intense as the reaction proceeded. The alkylation was rapid and by all indications was complete within 15 min. The reflux temperature was maintained for 1–2 hr and the cooled mixture then diluted with water. The solid products were crystallized from alcohol or a mixture of alcohol and DMF.

Uracil (0.2 mol) and barbituric acid (0.2 mol) in HOAc were separately heated with 0.2 mol of 10,11-dihydro-5*H*-dibenzo[*a,d*]-cyclohepten-5-ol and 20 g of boron trifluoride etherate. After 3–5 hr the products were isolated as described above and crystallized from alcohol.

2-Diarylmethylmalondiamides (30 and 31) (Table IV). Malondiamide (0.05 mol) and the appropriate diarylcarbinol (0.05 mol) were dissolved in 20 ml of hot 100% formic acid. Five drops of boron trifluoride etherate were added and the solution was heated under reflux for 10–12 min and then cooled. The solid product, precipitated by adding cold water, was washed with water and with ether and then crystallized from alcohol.

2-Diarylmethyl-, 2-(Xanthen-9-yl)-, and 2-Triphenylmethylmalononitriles (32–35) (Table IV). The diarylmethylmalondiamides (30 and 31) previously decribed were dehydrated by heating 0.1 mol of the diamide with 35–45 ml of $POCl_3$ in 25 g of acetamide for 3 hr at the refluxing temperature. The reaction mixture was poured onto ice and extracted into ether. The ether solution was washed with water, dried, and evaporated to yield the crystalline products (32 and 33).

Malononitrile (0.11 mol) was heated with triphenylcarbinol (0.1 mol) or with xanthen-9-ol (0.1 mol) in 50 ml of acetic acid. The reaction with xanthen-9-ol was complete in about 2 min, while the mixture containing triphenylcarbinol was heated for 8 hr. The cooled mixtures were added to water and the precipitated solids then crystallized from benzene.

Cyclizations of 2-(Diphenylmethyl)- and 2-(2,4-Dichloro)diphenylmethylmalondiamides (12 and 13) (Table V). The 2-diarylmethylmalondiamide, 30 and 31 (0.1 mol), was heated in a mixture of formamide and DMSO containing 2.2 molar equivalents of either potassium *tert*-butoxide, sodium methylate, or sodium hydroxide. The products were precipitated by adding very dilute HCl. The 5-diarylmethyl-4,6-dihydroxypyrimidines were separated from unreacted 2-diarylmethylmalondiamides by crystallization from alcohol.

Registry No.—**3**, 40016-23-7; **4**, 50278-30-3; **5**, 50278-31-4; **6**, 50278-32-5; **7**, 50278-33-6; **8**, 50454-83-6; **9**, 50278-34-7; **10**, 50278-35-8; **11**, 50278-36-9; **12**, 50278-37-0; **13**, 50278-38-1; **14**, 50278-39-2; **15**, 26920-22-9; **16**, 50278-41-6; **17**, 50278-42-7; **18**, 50278-43-8; **19**, 50278-44-9; **20**, 50278-45-0; **21**, 50278-46-1; **22**, 50454-84-7; **23**, 50278-47-2; **24**, 50278-48-3; **25**, 50278-49-4; **26**, 50278-50-7; **27**, 50278-51-8; **28**, 50278-52-9; **29**, 50278-53-0; **30**, 13023-11-5; **31**, 50278-55-2; **32**, 1846-19-1; **33**, 50278-57-4; **34**, 6235-15-0; **35**, 50278-59-6; 2-hydroxypyrimidine, 2209-57-6; 4-hydroxypyrimidine, 4562-27-0; 2-thiopyrimidine, 1450-85-7.

References and Notes

(1) I. Tanaka and T. Sadatome, Japanese Patent 4146 (1962); *Chem. Abstr.*, **59**, 2833a (1963).
(2) R. Adams, J. Hine, and J. Campbell, *J. Amer. Chem. Soc.*, **71**, 387 (1949).
(3) J. Ancizar-Sordo and A. Bistrzycki, *Helv. Chim. Acta*, **14**, 141 (1931).
(4) E. Sawicki and V. T. Oliverio, *J. Org. Chem.*, **21**, 183 (1956).
(5) G. Illari, *Gazz. Chim. Ital.*, **67**, 434 (1937); *Chem. Abstr.*, **32**, 12615 (1938).
(6) L. Monti and M. Delitala, *Gazz. Chim. Ital.*, **72**, 520 (1942); *Chem. Abstr.*, **38**, 45995 (1944).
(7) G. Illari, *Gazz. Chim. Ital.*, **68**, 103 (1938); *Chem. Abstr.*, **32**, 6242 (1938).
(8) D. J. Brown, "The Pyrimidines," Interscience, New York, N. Y., 1962, p 7.
(9) J. B. Campbell, C. W. Whitehead, T. J. Kress, and L. L. Moore, presented at the 4th Conference on Catalytic Hydrogenation and Analogous Pressure Reactions. New York Academy of Sciences, 1972.
(10) Satisfactory microanalytical data were obtained for the compounds in Tables I–IV.

Reactions of Diarylmethyl Cations with Aminopyrimidines

Calvert W. Whitehead* and Celia A. Whitesitt

The Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana 46206

Received October 12, 1973

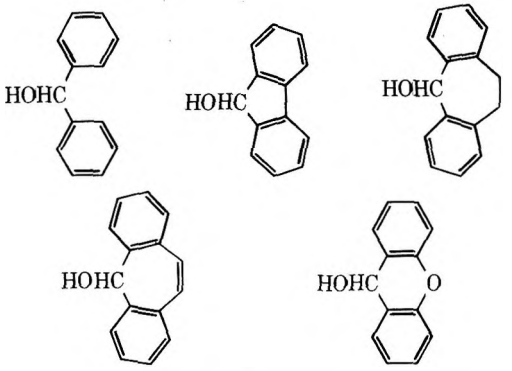
The reactions of diarylmethyl and dibenzomethyl cations with aminopyrimidines were investigated to determine the relative reactivities of the pyrimidine nucleophilic centers. While diarylmethyl cations reacted at the amine nitrogen of 2-aminopyrimidine, the diphenylmethyl cation reacted at both amine nitrogens of 4,6-diaminopyrimidine. Condensed dibenzomethyl cations reacted with 2-aminopyrimidine at the 2-amine nitrogen and at the 5-carbon position. The 9-xanthene cation reacted only at the 5 position of 4,6-diaminopyrimidine to yield 4,6-diamino-5-xanthen-9-ylpyrimidine. The relative affinity for these two positions is discussed. The 2-amino-4,6-dichloropyrimidine, substituted at the 5 position by diarylmethyl cations with accompanying hydrolysis of one chlorine, yields 2-amino-6-chloro-5-(diarylmethyl)-4-hydroxypyrimidines. A novel amino displacement of a 2-hydroxy group was apparently facilitated by the presence of the 5-(diphenylmethyl) group. Diphenylmethyl cation reacted with 4-amino-6-chloropyrimidine, followed by hydrolysis of the chlorine, to yield a mixture of 4-amino-5-(diphenylmethyl)-6-hydroxypyrimidine and 4-[(diphenylmethyl)amino]-6-hydroxypyrimidine.

Investigations in these laboratories have shown that 5-(diarylmethyl)pyrimidines have important antimicrobial as well as plant growth regulating properties.[1,2] Explorations into possible novel synthetic routes to these compounds led to this study of aralkylations of pyrimidines. Electrophilic substitutions by arylmethyl cations were shown, in the previous paper, to occur at the 5-carbon atom when the electron density of that position was enriched by hydroxy groups adjacent to nuclear nitrogens. While amino groups have electronic effects qualitatively similar to hydroxy groups, all previously reported alkylations of aminopyrimidines occurred at a nitrogen atom.[3,4]

Substitutions of aminopyrimidines by diarylmethyl cations are not only influenced by the electron densities of the nucleophilic centers but also by the nature of the attacking carbonium ion. Aminopyrimidines were allowed to

react with an appropriate diarylcarbinol in boiling glacial acetic acid. The compounds 2-aminopyrimidine and 2-amino-4,6-dimethylpyrimidine reacted with benzhydrol, 4-chlorobenzhydrol, 2-methoxybenzhydrol, and 3,4,5-trimethoxybenzhydrol to give the corresponding 2-[(diphenylmethyl)amino]- or 2-substituted-[(diphenylmethyl)amino]-pyrimidines, compounds **1–12** (Table I). The nmr data were consistent with the assigned structures, and tlc of the reaction mixtures indicated they were the only products formed. Addition of bromine to an acetic acid solution of 2-[(diphenylmethyl)amino]pyrimidine readily yielded 5-bromo-2-[(diphenylmethyl)amino]pyrimidine (**13**). Triphenylcarbinol failed to react with 2-aminopyrimidine after 18 hr.

Condensed dibenzomethyl cations, depending upon their structure, react with 2-aminopyrimidine at either the 2-amino nitrogen or 5-carbon position to give a mixture of two products, or they react exclusively at the 5-carbon position. Xanthen-9-ol and 5*H*-dibenzo[*a*,*d*]cyclohepten-5-ol reacted only at the 5 position to yield, respectively, 2-*amino-5-xanthen-9-ylpyrimidine* (**14**) and 2-amino-5-(5*H*-dibenzo[*a*,*d*]cyclohepten-5-yl)pyrimidine (**15**). When reacted with 2-aminopyrimidine, 10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepta-1,4-dien-5-ol yielded a mixture of 2-(10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepta-1,4-dien-5-ylamino)pyrimidine (**6**) and 2-amino-N^2,5-bis(10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepta-1,4-dien-6-yl)-pyrimidine (**16**). In the presence of excess 2-aminopyrimidine, **6** was formed exclusively. Reacting slowly with only the 2-amino group, 9-hydroxyfluorene gave after 24 hr starting material and 2-[(fluoren-9-yl)amino]pyrimidine (**1**) in 8% yield. The relative specificity for the 2-amino or 5-carbon position appears below.



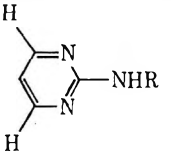
2-amino position ⟷ 5-carbon position

Benzhydrol reacted at both amino groups of 4,6-diaminopyrimidine to give a small yield of 4,6-bis[(diphenylmethyl)amino]pyrimidine (**17**). An nmr spectrum of the crude reaction mixture indicated the presence of unreacted 4,6-diaminopyrimidine. Xanthen-9-ol reacted with 4,6-diaminopyrimidine only at the 5 position to give 4,6-diamino-5-xanthen-9-ylpyrimidine (**18**) in good yield, but after 64 hr 9-hydroxyfluorene failed to react with 4,6-diaminopyrimidine. Xanthen-9-ol is oxidized completely to xanthen-9-one when dissolved in acetic acid at room temperature and allowed to stand for 15 min. Reactions of *xanthen-9-ol with 2-aminopyrimidine or with* 4,6-diaminopyrimidine must be completed rapidly upon contact.

Pyrimidine and pyrimidine sulfate each decomposed when heated in glacial acetic acid with benzhydrol. The only isolated product was (diphenylmethyl)acetamide. Xanthen-9-ol failed to react with pyrimidine at lower temperatures, and xanthen-9-one was obtained.

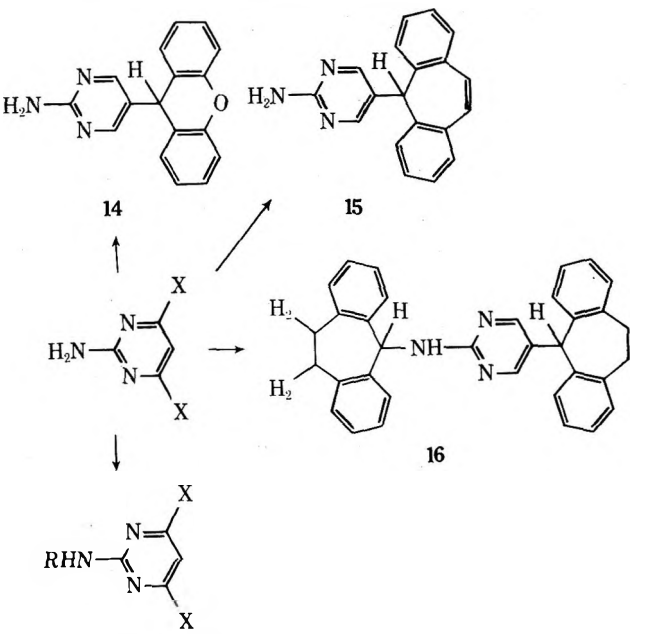
Both benzhydrol and 2-methoxybenzhydrol reacted at the 5 position of 2-amino-4,6-dichloropyrimdine. One of the chlorine atoms of 2-amino-4,6-dichloropyrimidine was

Table I
2-[(Diarylmethyl)amino]pyrimidines



No.	R	R_1	% yield[a]	Mp, °C[b,c]
1	$C_{14}H_{11}$[d]	H	8	200–201
2	$(4\text{-}ClC_6H_4)_2CH$	H	36	179–180
3	$4\text{-}ClC_6H_4C_6H_5CH$	H	49	127
4	$(C_6H_5)_2CH$	H	58	160[e]
5	$2\text{-}CH_3OC_6H_4C_6H_5CH$	H	50	149
6	$C_{15}H_{13}$[f]	H	71	175–177
7	$(4\text{-}ClC_6H_4)_2CH$	CH_3	21	125–127
8	$4\text{-}ClC_6H_4C_6H_5CH$	CH_3	31	118
9	$(C_6H_5)_2CH$	CH_3	62	126–127
10	$2\text{-}CH_3OC_6H_4C_6H_5CH$	CH_3	50	165–166
11	$3,4,5\text{-}(CH_3O)_3C_6H_2C_6H_5CH$	H	71	150
12	$3,4,5\text{-}(CH_3O)_3C_6H_2C_6H_5CH$	CH_3	51	158–59

[a] All yields were determined from analytically pure compounds. [b] The melting points are corrected. [c] Satisfactory analytical data (±0.4% for C, H, N, etc.) were reported for all new compounds listed in the paper. [d] Fluoren-9-yl. [e] Lit. mp 145–246° (**19**). [f] 10,11-Dihydro-5*H*-dibenzo[*a*,*d*]-cyclohepta-1,4-dien-5-yl.



1–12, X = H and CH_3

R = fluoren-9-yl (X = H only); $(4\text{-}ClC_6H_4)_2CH$; $(4\text{-}ClC_6H_4)(C_6H_5)CH$; $(C_6H_5)_2CH$; $(2\text{-}CH_3OC_6H_4)(C_6H_5)CH$; 10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepta-1,4-dien-5-yl (X = H only); $(3,4,5\text{-}(CH_3O)_3C_6H_2)(C_6H_5)CH$

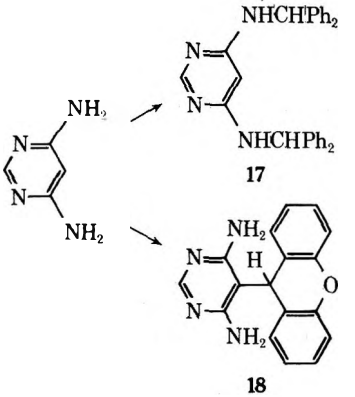
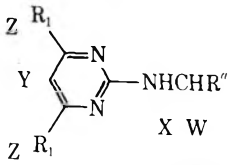


Table II
Nmr Data for the [(2-Diarylmethyl)amino]pyrimidines



Compd no.	Chemical shifts δ, ppm[b] R1	W[d]	X[d]	Y	Z
1[c]	H	6.31	7–8	6.69[f]	8.35[d]
2	H	6.40	7.57	6.53[f]	8.17[d]
3	H	6.34	g	6.37[f]	7.94[d]
4	H	6.43	g	6.28[f]	7.87[d]
5	H	6.61	g	6.33[f]	8.02[d]
6	H	6.73	g	6.29[f]	8.05[d]
7	CH_3	6.45	7.73	6.28[e]	2.23[e]
8	CH_3	6.38	5.76	6.28[e]	2.20[e]
9	CH_3	6.51	g	6.20[e]	2.17[e]
10	CH_3	6.67	6.11	6.23[e]	2.21[e]
11	H	6.38	7.92	6.35[f]	7.87[d]
12	CH_3	6.35	6.73	6.28[e]	2.23[e]

[a] R represents two aryl groups (compounds **2–5, 7–12**) or two condensed aryl groups (compounds **1** and **6**). [b] The solvent was $CDCl_3$, unless otherwise designated. [c] Solvent was $(CD_3)_2SO$. [d] Doublet. [e] Singlet. [f] Triplet. [g] Under aromatic region.

hydrolyzed during the substitution reaction to give 2-amino-6-chloro-5-(diphenylmethyl)-4-hydroxypyrimidine (**19**) and 2-amino-6-chloro-4-hydroxy-5-[2-methyoxy(diphenylmethyl)]pyrimidine (**20**), respectively. When warmed in acetic acid, 2,4,6-trichloropyrimidine did not react with xanthen-9-ol and the trichloropyrimidine was not hydrolyzed under these conditions. This result and the fact that 2-amino-6-chloro-4-hydroxypyrimidine reacted with benzhydrol to yield compound **19** suggest that one chlorine of 2-amino-4,6-dichloropyrimidine is hydrolyzed before substitution occurs. The hydrolysis of one of the chloro groups of 2-amino-4,6-dichloropyrimidine and the unreactivity of the trichloropyrimidine might also be attributed to a greater degree of protonation in the 2-aminopyrimidine. Since **19**, when treated with nitrous acid,

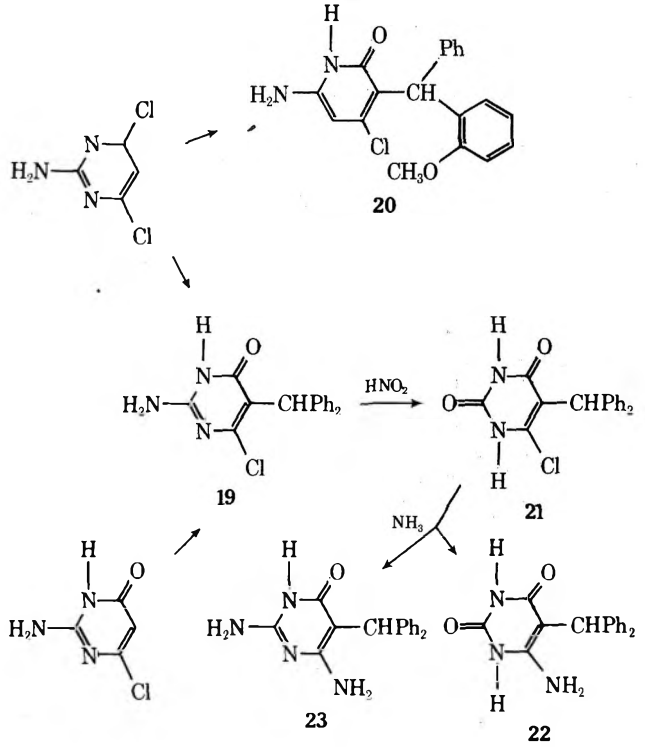
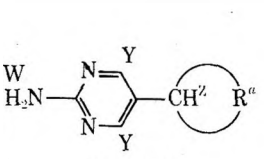
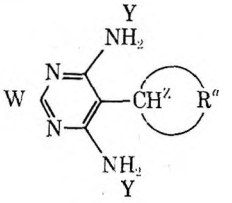


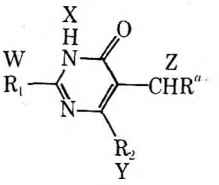
Table III
Nmr Data for [Amino(diarylmethyl)]pyrimidines



14 and 15



18

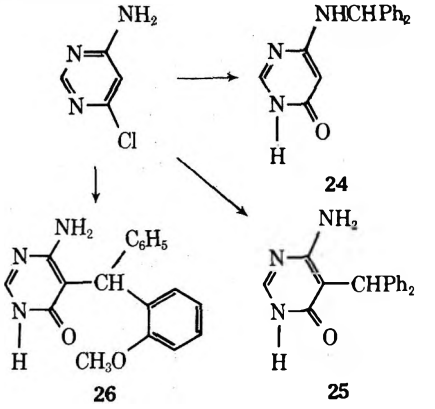


19-23

Compd no.	Chemical shifts δ, ppm R1	R2	W	X[b]	Y	Z[g]
14[c]			6.05		8.05[g]	5.16
15[c]			11.50		7.63[g]	5.44
18[d]			8.34[g]			5.92
19[e]	NH_2	Cl	6.97[b]	11.18		5.70
20[f]	NH_2	Cl	6.57[b]	11.00		6.00
21[c]	HO	Cl	6.62	6.62		5.70
22[e]	HO	NH_2	9.93[b]	10.38	5.78[b]	5.47
23[f]	NH_2	NH_2	5.34[b]	9.93	6.11[b]	5.61

[a] R represents two aryl groups (compounds **19–23**) or two condensed aryl groups (compounds **14, 15,** and **18**). [b] Broad signal. [c] Solvent was $CDCl_3$ + $(CD_3)_2SO$. [d] Compound was soluble only in trifluoroacetic acid; the NH_2 proton signals could not be observed. [e] Solvent was $(CD_3)_2SO$. [f] Solvent was $CDCl_3$. [g] Singlet.

yielded 4-chloro-2,6-dihydroxy-5-(diphenylmethyl)pyrimidine (**21**), the possibility that the diphenylmethyl group might have been on the 2-amino position was eliminated. When **21** was treated with alcoholic ammonia at 150°, the 6-chlorine was displaced with NH_2 to yield 6-amino-5-(diphenylmethyl)-2,4-dihydroxypyrimidine (**22**). Unexpectedly the 2-hydroxy group exchanged with ammonia to give a second product, 2,6-diamino-5-(diphenylmethyl)-4-hydroxypyrimidine (**23**). By comparing the nmr spectra of compounds **19** and **23**, it became obvious that the diarylmethyl group was on the 5-carbon. Exchange of the 2-hydroxy group with ammonia is facilitated by the presence of this 5-(diphenylmethyl) group, since 6-aminouracil remained unchanged when treated with alcoholic ammonia at 150°. The reaction of benzhydrol with 4-amino-6-chloropyrimidine yielded a mixture of 4-amino-5-(diphenylmethyl)-6-hydroxypyrimidine (**24**) and 4-[(diphenylmethyl)amino]-6-hydroxypyrimidine (**25**). Hydrolysis of the 6-chlorine also occurred in the reaction of 4-amino-6-chloropyrimidine with 2-methoxybenzhydrol, but only one prod-



uct, 4-amino-6-hydroxy-5-[2-methoxy(diphenylmethyl)]pyrimidine (26) was isolated.

Confirmation of Structures by Nmr Spectra

Signals for protons at the 4, 5, and 6 positions of compounds 1–6 and 11, as well as signals for protons of the 4- and 6-methyl groups of compounds 7–10 and 12, are given in Table II. Singlet signals at 6.20–6.28 ppm (Y, Table II) are from protons at position 5 when methyl groups are at both the 4 and 6 positions. Protons at positions 4 and 6 split the signals for protons at position 5 by 5 Hz, and the resulting triplets have centers at 6.28–6.53 ppm. Protons at positions 4 and 6 are less shielded and have doublet signals with centers at 7.87–8.17 ppm, split 5 Hz by a proton at position 5. The signal for 4- and 6-methyl protons occurs at 2.17 and 2.23 ppm (Z, Table II).

The doublet signals between 6.34 and 6.67 ppm (Y, Table II) for the CH protons of the diarylmethyl groups are split 8 Hz by the adjacent 2-amino proton.

The high field position of signals at 5.16–6.00 ppm (Z, Table III) and their singlet character show that compounds 14–19 and 21–23 have the diarylmethyl group at the 5 position.

Experimental Section

All melting points are corrected. The nmr spectra were determined by the Varian HA-60 instrument.

2-[(Diarylmethyl)amino]pyrimidines (Table I, Compounds 1–12). 2-Aminopyrimidine or 2-amino-4,6-dimethylpyrimidine (0.1 mol) and 0.1 mol of the appropriate diarylcarbinol were dissolved in 100 ml of glacial acetic acid. The solution was heated under reflux for 8 to 24 hr, cooled, and poured into water. The solid products were washed thoroughly with water, and the oily products were extracted into ether. The ether solution was washed with water, concentrated, and eventually crystallized. All the products were purified by crystallizing from EtOAc–petroleum ether.

5-Bromo-2-[(diphenylmethyl)amino]pyrimidine (13). After 2-[(diphenylmethyl)amino]pyrimidine (10 g, 0.038 mol) was dissolved in 50 ml of acetic acid at room temperature, bromine in acetic acid was added dropwise until the bromine color persisted; the mixture was added to 500 ml of water. The insoluble product was collected and recrystallized from EtOAc, mp 167°, yield 2.2 g (17%).

The nmr signal in dimethyl sulfoxide solution for the methyl proton of the diphenylmethyl group is a doublet with peaks at 6.3 and 6.45 ppm. The signal for the 4 and 6 protons of the pyrimidine ring is a singlet at 8.24 ppm, which indicates the 5 proton has been substituted by bromine.

Anal. Calcd for $C_{17}H_{14}BrN_3$: C, 60.01; H, 4.14. Found: C, 60.17; H, 4.25.

2-Amino-5-xanthen-9-ylpyrimidine (14). 2-Aminopyrimidine (0.1 mol, 9.5 g) and xanthen-9-ol (0.1 mol, 19.8 g) were added to 80 ml of glacial acetic acid and heated to refluxing temperature for 18 hr. The solution was added to 400 ml of water. The insoluble material was shown to be a mixture. It was separated on a chromatographic column of 1 kg of Grace silica gel, grade 950, with $CHCl_3$ and yielded 4.3 g (15%) of 14, mp 213°.

Anal. Calcd for $C_{17}H_{13}N_3O$: C, 74.16; H, 4.73; N, 15.26. Found: C, 74.12; H, 4.87; N, 15.26.

The substitution reaction was slow enough to allow xanthen-9-ol to be partially oxidized to xanthen-9-one. Both xanthen-9-one and unreacted 2-aminopyrimidine were isolated from this chromatography.

2-Amino-5-(5*H*-dibenzo[*a*,*d*]cyclohepten-5-yl)pyrimidine (15). 2-Aminopyrimidine (0.1 mol, 9.5 g) and 5*H*-dibenzo[*a*,*d*]cyclohepten-5-ol (0.1 mol, 20.8 g) were dissolved in 100 ml of glacial acetic acid and heated under reflux for 28 hr. The mixture was poured into water, and the solid was collected by filtration. The product was crystallized from alcohol, yield 16.3 g (57%), mp 241°.

Anal. Calcd for $C_{19}H_{15}N_3$: C, 79.97; H, 5.30. Found: C, 80.00; H, 5.40.

2-(10,11-Dihydro-5*H*-dibenzo[*a*,*d*]cyclohepta-1,4-dien-5-ylamino)pyrimidine (6) and N^2,5-Bis(10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepta-1,4-dien-5-yl)-2-aminopyrimidine (16). 10,11-Dihydro-5*H*-dibenzo[*a*,*d*]cycloheptа-1,4-dien-5-ol (0.2 mol) and 2-aminopyrimidine (0.2 mol) were dissolved in 200 ml of glacial acetic acid and heated to refluxing temperature for 64 hr. The cooled mixture was added to water, and the insoluble solid was collected. Tlc showed the crude solid to be a mixture of two compounds. These were characterized by nmr as compound 6 (80%) and compound 16 (20%). The crude mixture was developed on a silica gel column ($CHCl_3$) to yield 16 (8.4%), mp 146° (crystallized from EtOAc).

Anal. Calcd for $C_{34}H_{29}N_3$: C, 85.14; H, 6.10; N, 8.76. Found: C, 85.14; H, 6.36; N, 8.75.

When the above reaction was repeated with a 20% excess of 2-aminopyrimidine, the precipitated solid yielded only compound 6 (Table I) (EtOAc).

4,6-Bis[(diphenylmethyl)amino]pyrimidine (17). 4,6-Diaminopyrimidine (0.1 mol) and benzhydrol (0.1 mol) were added to 150 ml of glacial acetic acid, heated to refluxing temperature for 24 hr, cooled, and added to water. The oil partly crystallized after standing for several days in fresh water. The solid was collected on a suction funnel and recrystallized from EtOAc, yield 2.1 g (9.6% based on the benzhydrol), mp 234°.

Anal. Calcd for $C_{30}H_{26}N_4$: C, 81.41; H, 5.92; N, 12.66. Found: C, 81.24; H, 5.91; N, 12.89.

4,6-Diamino-5-xanthen-9-ylpyrimidine (18). A solution of xanthen-9-ol (19.8 g, 0.1 mol) and 4,6-diaminopyrimidine (11 g, 0.1 mol) in 150 ml of glacial acetic acid was heated to refluxing temperature for 24 hr, then cooled and poured into cold water. The solid product was collected, and a sample was developed on tlc with EtOAc. Only one spot was evident after exposure to iodine vapor. The product was recrystallized from EtOH, mp 288° dec, yield 61%.

Anal. Calcd for $C_{17}H_{14}N_4O$: C, 70.33; H, 4.86; N, 19.30. Found: C, 70.62; H, 4.55; N, 19.05.

2-Amino-6-chloro-5-(diphenylymethyl)-4-hydroxypyrimidine (19). 2-Amino-4,6-dichloropyrimidine (0.1 mol, 16.4 g) and benzhydrol (0.1 mol, 18.4 g) were dissolved in 80 ml of glacial acetic acid, heated to refluxing temperature for 24 hr, and poured into 400 ml of water. The solid product was crystallized from EtOAc–petroleum ether and yielded 7.1 g (46%), mp 253°.

Anal. Calcd for $C_{17}H_{14}ClN_3O$: C, 65.48; H, 4.52; N, 13.47; Cl, 11.37. Found: C, 65.27; H, 4.69; N, 13.20; Cl, 11.42.

2-Amino-6-chloro-5-(diphenylmethyl)-4-hydroxypyrimidine was prepared in a similar manner from 2-amino-6-chloro-4-hydroxypyrimidine and benzyhydrol, mp 254°, yield 25%.

2-Amino-6-chloro-4-hydroxy-5[(2-methoxydiphenyl)methyl]-pyrimidine (20). 2-Amino-4,6-dichloropyrimidine (0.1 mol, 16.4 g) and 2-methoxybenzhydrol (0.1 mol, 21.4 g) were reacted in the manner described for the preparation of 19, yield 14%, mp 255–256°.

Anal. Calcd for $C_{18}H_{16}ClN_3O_2$: C, 63.24; H, 4.21; N, 12.29; Cl, 10.37. Found: C, 63.23; H, 4.83; N, 12.07; Cl, 10.38.

6-Chloro-5-(diphenylmethyl)-2,4-dihydroxypyrimidine (21). To a cooled solution (20% of 2-amino-6-chloro-5-(diphenylmethyl)-4-hydroxypyrimidine (0.08 mol, 25.0 g) in a minimum amount of glacial acetic acid, was added, gradually, sodium nitrite (0.17 mol, 11.72 g), and the solution was stirred for 18 hr. One liter of water was added to the solution. The product was collected and crystallized from EtOAc–petroleum ether, mp 238°, yield 15.7 g (62.19%).

Anal. Calcd for $C_{17}H_{13}ClN_2O_2$: C, 65.28; H, 4.18; N, 8.97; Cl, 11.33. Found: C, 65.45; H, 4.22; N, 9.05; Cl, 11.26.

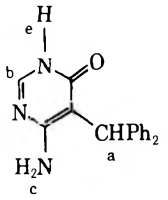
6-Amino-5-(diphenylmethyl)-2,4-dihydroxypyrimidine (22) and 2,4-Diamino-5-(diphenylmethyl)-6-hydroxypyrimidine (23). 6-Chloro-5-(diphenylmethyl)-2,4-dihydroxypyrimidine (0.02 mol. 7.0 g) was dissolved in excess alcoholic ammonia and heated at 150° for 12 hr in a bomb. The solution was evaporated. The resulting solid was shown by nmr to be a mixture of 6-amino-5-(diphenylmethyl)-2,4-dihydroxypyrimidine (30%) and 2,4-diamino-5-(diphenylmethyl)-6-hydroxypyrimidine (70%). The latter was separated from the mixture by crystallization from EtOAc, mp 248°, with characteristic nmr signals as presented in Table III. This compound (23) had an nmr signal, in deuterated chloroform, identical with the nmr signal of 2,4-diamino-5-(diphenylmethyl)-6-hydroxypyrimidine in deuterated chloroform. Compound 23 gave a mass ion of 292 (calculated 292) as determined on the Varian Mat 731 mass spectrometer.

6-Amino-5-(diphenylmethyl)-2,4-dihydroxypyrimidine was also isolated with good recovery of the amount indicated by the spectrum, mp 324°.

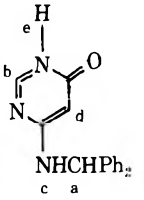
Anal. Calcd for $C_{17}H_{15}N_3O_2$: C, 69.91; H, 5.15; N, 14.32. Found: C, 69.70; H, 5.27; N, 14.20.

4-Amino-5-(diphenylmethyl)-6-hydroxypyrimidine (24) and 4-(Diphenylmethyl)amino-6-hydroxypyrimidine (25). 4-Amino-6-chloropyrimidine (0.1 mol, 13 g) and benzhydrol (18.4 g) were

added to 80 ml of glacial acetic acid and heated under reflux for 16 hr. The product was precipitated with water and was crystallized from dilute alcohol. The C, H, and N analyses were correct for $C_{17}H_{15}N_3O$, but the nmr spectra indicated a 50:50 mixture of 4-amino-5-(diphenylmethyl)-6-hydroxypyrimidine and 4-[(diphenylmethyl)amino]-6-hydroxypyrimidine. The mixture was separated on a silica gel column with $CHCl_3$. Each compound was characterized by its nmr taken in dimethyl sulfoxide; the assignments are shown below.



δ, ppm
a, 5.66
b, 7.82
c, 5.97
e, 11.75



δ, ppm
a, 6.03
b, 7.87
c, 7.80
d, 5.22
e, 11.75

4-Amino-6-hydroxy-5-[2-methoxy(diphenylmethyl)]pyrimidine (26). 4-Amino-6-chloropyrimidine (0.1 mol, 13.0 g) and 2-methoxybenzhydrol (0.1 mol, 21.4 g) were added to 80 ml of acetic acid and heated under reflux for 16 hr. The product was precipitated by adding the mixture to 400 ml of water. It was purified by crystallization from EtOAc–petroleum ether, yield 14 g (43%), mp 293° dec.

Anal. Calcd for $C_{18}H_{17}N_3O_2$: C, 70.34; H, 5.58; N, 13.67. Found: C, 70.29; H, 5.81; N, 13.88.

Acknowledgments. The authors are grateful for the able assistance of Dr. Harold E. Boaz (deceased) in interpreting nmr data, to Mr. Larry A. Spangle and coworkers for nmr data, and to Mr. George M. Maciak and coworkers for analytical results.

Registry No.—**1**, 50259-14-8; **2**, 50259-15-9; **3**, 50259-16-0; **4**, 50259-17-1; , 50259-18-2; **6**, 50259-19-3; **7**, 50259-20-6; **8**, 50259-21-7; **9**, 50259-22-8; **10**, 50259-23-9; **11**, 50259-24-0; **12**, 50430-99-4; **13**, 50259-25-1; **14**, 50259-26-2; **15**, 50259-27-3; **16**, 50259-28-4; **17**, 50259-29-5; **18**, 50431-00-0; **19**, 50259-30-8; **20**, 50259-31-9; **21**, 50259-32-0; **22**, 50259-33-1; **23**, 50259-34-2; **24**, 50259-35-3; **25**, 50259-36-4; **26**, 50259-37-5; 2-aminopyrimidine, 109-12-6; 2-amino-4,6-dimethylpyrimidine, 767-15-7; 4,6-diaminopyrimidine, 2434-56-2; 2-amino-4,6-dichloropyrimidine, 56-05-3; 2-amino-6-chloro-5-(diphenylmethyl)-4-hydroxypyrimidine, 50259-38-6; 6-chloro-5-(diphenylmethyl)-2,4-dihydroxypyrimidine, 50259-39-7; 4-amino-6-chloropyrimidine, 5305-59-9.

References and Notes

(1) I. F. Brown, Jr., J. W. Whaley, H. M. Taylor, and E. M. Van Heyningen, *Phytopathology*, **57**, 805 (1967).
(2) P. L. Thayer, D. H. Ford, and H. R. Hall, *Phytopathology*, **57**, 833 (1967).
(3) I. Tanaka and T. Sadatome, Japanese Patent 4146 (1962); *Chem. Abstr.*, **59** 2833a (1963).
(4) D. J. Brown, "The Pyrimidines," Interscience, New York, N. Y., 1962, pp 24, 311, 380.

Dimetalated Heterocycles as Synthetic Intermediates. V. Dianions Derived from Certain 2-Hydroxy-4-methylpyrimidines, 2-Amino-4-methylpyrimidines, and Related Compounds†[1]

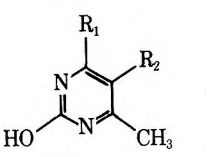
Thomas P. Murray, James V. Hay, David E. Portlock, and James F. Wolfe*

Department of Chemistry, Virginia Polytechnic Institute and State University, Blacksburg, Virginia 24061

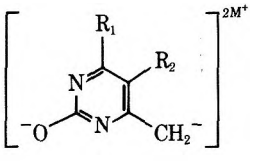
Received August 8, 1973

A convenient new method, involving dianion intermediates, has been developed for side-chain elaboration of 2-hydroxy-4-methylpyrimidines (**1a–c**), 2-anilino-4-methyl-6-phenylpyrimidine (**15a**), 2-amino-4-methylpyrimidine (**15b**), and 2-methyl-4(3*H*)-quinazolinone. The dianions, prepared by twofold metalation of the parent heterocycles with *n*-butyllithium in THF–hexane or sodium amide in liquid ammonia, reacted with benzyl chloride and carbonyl compounds to selectively establish exocyclic carbon–carbon bonds. Reaction of 4-hydroxy-2,6-dimethylpyrimidine (**8**) with 2 equiv of *n*-butyllithium produced a mixture of isomeric dianions (**9a–b**) in which **9a**, resulting from abstraction of a proton from the 4-methyl position, predominated.

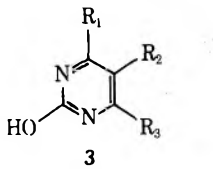
Although certain 2-hydroxy-, 2,4-dihydroxy-, 2-amino-, and 2,4-diaminopyrimidines containing a nuclear methyl substituent have been reported to undergo active hydrogen reactions such as aldol and Claisen condensations,[2] such processes generally appear to involve only low, equilibrium-controlled concentrations of carbanionic species. Recently, Klein and Fox[3] have used the Wittig reaction of phosphonium salt **4** with several aldehydes for the synthesis of 6-substituted uracils. We now describe a simple new method for elaboration of the methyl group of 2-hydroxypyrimidines (**1**) which avoids the necessity for hydroxyl masking or the preparation of phosphonium salts such as **4**. The procedure is based on initial generation of dianions (**2**), followed by treatment with various electrophilic reagents to form the appropriate C-substituted derivatives (**3**). Dianions derived from pyrimidines possessing other arrangements of hydroxyl and methyl, as well as those having suitably positioned mercapto and methyl, anilino and methyl, or amino and methyl groups, can be formed and utilized in a similar fashion.



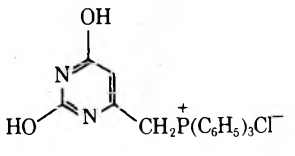
1a, $R_1 = CH_3$; $R_2 = C_6H_5$
b, $R_1 = C_6H_5$; $R_2 = H$
c, $R_1 = CH_3$; $R_2 = H$



2a, $R_1 = CH_3$; $R_2 = C_6H_5$
b, $R_1 = C_6H_5$; $R_2 = H$
c, $R_1 = CH_3$; $R_2 = H$
d, $R_1 = C_6H_5(CH_2)_2$; $R_2 = C_6H_5$



3



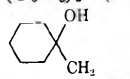
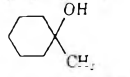
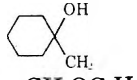
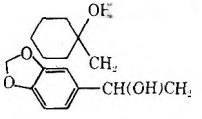
4

Results and Discussion

In an initial search for suitable basic reagents, the readily available 2-hydroxy-4,6-dimethyl-5-phenylpyrimidine

Table I

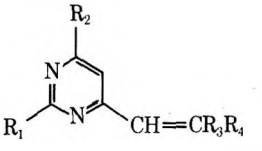
Reactions of Dianions with Electrophiles

Dianion (M)	Electrophile	Compd	R_1	R_2	R_3	Yield, %	Mp, °C
2a (Li)	Benzyl chloride	**3a**	CH_3	C_6H_5	$C_6H_5(CH_2)_2$	76	198–202[a]
2a (Na)	Benzyl chloride	**3a**	CH_3	C_6H_5	$C_6H_5(CH_2)_2$	75	202–204[a]
2a (Li)	Benzophenone	**3b**	CH_3	C_6H_5	$(C_6H_5)_2C(OH)CH_2$	89	144–146[b]
2a (Li)	Cyclohexanone	**3c**	CH_3	C_6H_5		52	148–150[c]
2a (Li)	Methyl benzoate	**3d**	CH_3	C_6H_5	$C_6H_5COCH_2$	69	324–327[b]
2d (Li)	Benzyl chloride	**3e**	$C_6H_5(CH_2)_2$	C_6H_5	$C_6H_5(CH_2)_2$	57	176–177[d]
2b (Li)	Benzyl chloride	**3f**	C_6H_5	H	$C_6H_5(CH_2)_2$	39	180–182[a]
2b (Na)	Benzyl chloride	**3f**	C_6H_5	H	$C_6H_5(CH_2)_2$	65	180–182[a]
2b (Li)	Benzophenone	**3g**	C_6H_5	H	$(C_6H_5)_2C(OH)CH_2$	79	166–167[e]
2b (Na)	Benzophenone	**3g**	C_6H_5	H	$(C_6H_5)_2C(OH)CH_2$	68	166–167[e]
2b (Li)	Cyclohexanone	**3h**	C_6H_5	H		44	183–184[b]
2b (Li)	Anisaldehyde	**3i**	C_6H_5	H	p-$CH_3OC_6H_4CH(OH)CH_2$	68	255–260[b]
2b (Li)	Heptaldehyde	**3i**	C_6H_5	H	$CH_3(CH_2)_5CH(OH)CH_2$	41	138–140[a]
2b (Li)	Methyl benzoate	**3k**	C_6H_5	H	$C_6H_5COCH_2$	64	233–234.5[b]
2b (Li)	Ethyl acetate	**3l**	C_6H_5	H	CH_3COCH_2	63	209–211[a]
2c (Li)	Benzophenone	**3m**	CH_3	H	$(C_6H_5)_2C(OH)CH_2$	21	98–103[a]
2c (Li)	3,4,5-Trimethoxybenzaldehyde	**3n**	CH_3	H	$3,4,5\text{-}(CH_3O)_3C_6H_2CH(OH)CH_2$	10	119–121[c]
12 (Li)	Benzyl chloride	**13a**	$C_6H_5(CH_2)_2$			58	208–210[b,f]
12 (Li)	Ethyl bromide	**13b**	$CH_3(CH_2)_2$			57	193.5–195[g,h]
12 (Li)	Acetophenone	**13c**	$C_6H_5C(OH)(CH_3)CH_2$			63	135–136[i]
12 (Li)	Benzophenone	**13d**	$(C_6H_5)_2C(OH)CH_2$			58	163–164[g]
12 (Li)	Anisaldehyde	**13e**	p-$CH_3OC_6H_4CH(OH)CH_2$			50	177.5–179[c]
16a (Li)	Benzyl chloride	**17a**	C_6H_5	C_6H_5	$C_6H_5(CH_2)_2$	70	90–92[a]
16a (Li)	Benzophenone	**17b**	C_6H_5	C_6H_5	$(C_6H_5)_2C(OH)CH_3$	90	149–152[b]
16a (Na)	Benzophenone	**17b**	C_6H_5	C_6H_5	$(C_6H_5)_2C(OH)CH_2$	38	149–152[b]
16a (Li)	3,4-Dichloro-4′-trifluoromethylbenzophenone	**17c**	C_6H_5	C_6H_5	$3,4\text{-}(Cl)_2C_6H_5C(OH)(4\text{-}CF_3C_6H_4)CH_2$	85	202–204[a,j]
16a (Li)	Cyclohexanone	**17d**	C_6H_5	C_6H_5		55	139–141[a]
16a (Li)	Anisaldehyde	**17e**	C_6H_5	C_6H_5	p-$CH_3OC_6H_4CH(OH)CH_2$	80	132–134[b]
16a (Li)	Heptaldehyde	**17f**	C_6H_5	C_6H_5	$CH_3(CH_2)_5CH(OH)CH_2$	40	175–177[c,j]
16b (Li)	Benzyl chloride	**17g**	H	H	$C_6H_5(CH_2)_2$	58	162–164[b,k]
16b (Na)	Benzyl chloride	**17g**	H	H	$C_6H_5(CH_2)_2$	11	162–164[b,k]
16b (Li)	Benzophenone	**17h**	H	H	$(C_6H_5)_2C(OH)CH_2$	70	193–195[a]
16b (Li)	Cyclohexanone	**17i**	H	H		54	197–199[a]
16b (Li)	Piperonal	**17j**	H	H		27	172–174[b]
16b (Li)	Heptaldehyde	**17k**	H	H	$CH_3(CH_2)_5CH(OH)CH_2$	37	103–104[a]

[a] Recrystallized from aqueous ethanol. [b] Recrystallized from ethanol. [c] Recrystallized from ethyl acetate. [d] Recrystallized from ethanol–2-propanol (1:1). [e] Crude product. [f] Lit. mp 209.5–210.5°: E. B. Marr and M. T. Bogert, *J. Amer. Chem. Soc.*, **57**, 729 (1935). [g] Recrystallized from ethyl acetate–hexane. [h] Lit. mp 200–201°: D. T. Zentmeyer and E. C. Wagner, *J. Org. Chem.*, **14**, 967 (1949). [i] Recrystallized from acetone–hexane. [j] Characterized as the HCl salt. [k] Lit.[11] mp 162–164°.

(**1a**)[4] was used as a model substrate for dianion formation. Since alkali amides and organolithium reagents had previously[4,5] been reported to be suitable for lateral metalation of a few methylpyrimidines not possessing a second active-hydrogen substituent, sodium amide and *n*-butyllithium complexed with *N,N,N′,N′*-tetramethylethylenediamine (TMEDA)[6] were tested for their ability to effect twofold deprotonation of **1a**. Treatment of **1a** with 2 molar equiv of *n*-butyllithium complexed with TMEDA in THF–hexane at 0° resulted in excellent conversion of **1a** into dianion **2a** (M = Li) as evidenced by deuteration and by alkylation with benzyl chloride to form **3a** (Table I). Dianion **2a** (M = Li) underwent carbonyl addition reactions with benzophenone and cyclohexanone to give carbinols **3b–c** in good yields, while acylation with methyl benzoate gave the highly enolic phenacylpyrimidine **3d**. Formation and benzylation of **2a** (M = Na) was also accomplished satisfactorily by means of 2 molar equiv of sodium amide in liquid ammonia. However, attempted condensation of disodio **2a** with cyclohexanone resulted mainly in enolization of the ketone. For this reason, the more covalent dilithio salts reported herein are recommended for reactions with aliphatic carbonyl compounds. Treatment of phenethylpyrimidine **3a** with 2 equiv of *n*-butyllithium–TMEDA afforded predominately dianion **2d** (M = Li) as shown by benzylation to form symmetrical derivative **3e**.

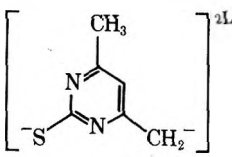
Next, it was demonstrated that a 5-phenyl substituent was not necessary for dianion formation and that TMEDA could also be eliminated without severely hampering the twofold ionization process. Thus, reaction of **1b** with 2 equiv of *n*-butyllithium followed by benzyl chloride afforded *C*-benzyl derivative **3f**. Further evidence for the presence of dianion **2b** (M = Li) was obtained by reactions with benzophenone, cyclohexanone, anisaldehyde, and heptaldehyde to form **3g–j**, respectively. Dehydration of carbinols **3g** and **3i** with *p*-toluenesulfonic acid (PTSA) in refluxing benzene afforded styryl derivatives **5a–b** in yields of 85 and 65%, respectively. Acylation of **2b** (M = Li) with methyl benzoate and ethyl acetate yielded pyrimidinyl ketones **3k–l**. Dianion **2b** (M = Na) could also be prepared by means of sodium amide in liquid ammonia, as shown by reactions with benzyl chloride and benzophenone to give **3f** and **3g** in yields comparable to those obtained with dilithio salt **2b**.



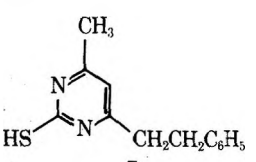
5a, R_1 = OH; R_2 = C_6H_5; R_3 = R_4 = C_6H_5
b, R_1 = OH; R_2 = C_6H_5; R_4 = *p*-$CH_3OC_6H_4$; R_4 = H
c, R_1 = OH; R_2 = CH_3; R_3 = R_4 = C_6H_5

While conversion of the hydrochloride salt of pyrimidine **1c** into dianion **2c** (M = Na) with 3 equiv of sodium amide in liquid ammonia was generally unsatisfactory, **2c** (M = Li) was generated, albeit in low concentrations, using 3 equiv of *n*-butyllithium complexed with TMEDA or 1,4-diazabicyclo[2.2.2]octane (Dabco).[7] Trapping experiments with benzophenone and 3,4,5-trimethoxybenzaldehyde in the presence of Dabco afforded adducts **3m–n**, the former of which was dehydrated with PTSA to give **5c**.

Reaction of 2-mercapto-4,6-dimethylpyrimidine with 2 equiv of *n*-butyllithium followed by benzyl chloride afforded a complex mixture of products from which **7** was isolated in 29% yield, thereby providing evidence for the intermediacy of dianion **6**. Pmr analysis of the crude product mixture indicated the presence of S-benzylated products also.



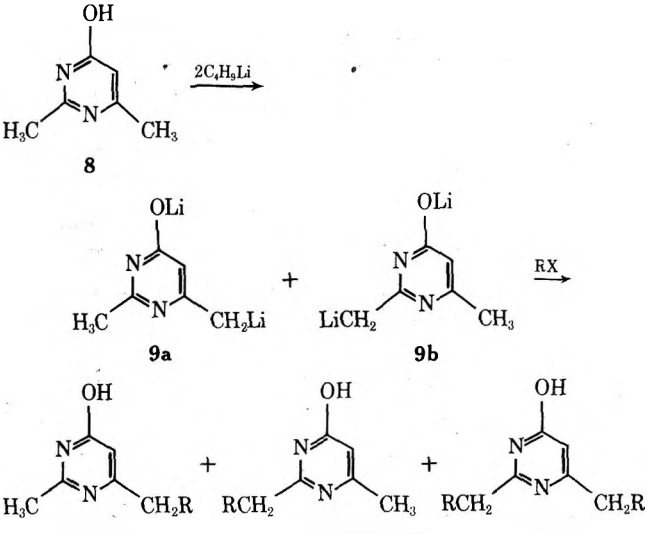
6



7

To ascertain if there was any preference for dianion formation at one or the other of two activated, but nonequivalent, methyl groups, 2,6-dimethyl-4-hydroxypyrimidine (**8**) was treated with 2 equiv of *n*-butyllithium and separate reaction mixtures were quenched with benzyl chloride and *n*-butyl bromide. Alkylation with benzyl chloride gave monoalkyl derivatives **10a–b** and dialkyl derivative **10c** in yields of 48, 13, and 7%, respectively, while alkylation with *n*-butyl bromide gave the corresponding mono- and dialkylation products **11a–c** in yields of 39, 18, and 8%, respectively (Scheme I). These results are consistent with predominant formation of dianion **9a**.[8] It seems unlikely that dialkylated products **10c** and **11c** arise through formation and alkylation of a dianion produced by ionization of both methyl groups but not the hydroxy function, or a trianion having both methyls and the hydroxyl ionized, since initial formation of such intermediates in the presence of 2 equiv of base should be cancelled by subsequent proton–metal exchange to form dianions **9a** and **9b**. Moreover, it was demonstrated that treatment of **8** with 3 equiv of *n*-butyllithium followed by benzyl chloride did not produce significantly higher yields of **10c** than those observed with 2 equiv of base. The most likely route to dialkylated products **10c** and **11c** therefore appears to involve initial C-alkylation of either **9a** or **9b** followed by proton–metal exchange between monoalkylated derivatives **10a–b** and **11a–b** (as the O–Li salts) and original dianions **9a–b** to form the isomeric dianions resulting from abstraction of methyl protons from **10a** or **10b** and **11a** or **11b**. Alkylation of these dianions then produces **10c** and **11c**.

Scheme I



8

9a **9b**

10a, R = $CH_2C_6H_5$ **10b**, R = $CH_2C_6H_5$ **10c**, R = $CH_2C_6H_5$
11a, R = *n*-C_4H_9 **11b**, R = *n*-C_4H_9 **11c**, R = *n*-C_4H_9

Although the foregoing results indicated that a 4- (or 6-) methyl substituent is more readily deprotonated than a 2-methyl group, we found that 2-methyl-4(3*H*)-quinazolinone, which may be regarded as analogous to a 4-hydroxy-2-methylpyrimidine, could be converted into dianion **12** by means of uncomplexed *n*-butyllithium. Subsequent condensations of **12** with benzyl chloride, ethyl bromide, acetophenone, benzophenone, and anisaldehyde resulted

JOC-32-1

EXPERIMENTAL SECTION

General. -- Melting points were obtained on a Thomas-Hoover apparatus in open capillaries and are uncorrected. Infrared spectra were obtained on either a Beckman *IR-5A* or *a Beckman IR 20A-X spectrophotometer*. Pmr spectra were obtained on a Varian A-60 or a JEOL JNM-PS-100 instrument with chemical shifts expressed in parts per million downfield from TMS internal standard. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn.; *M-H-W Laboratories, Garden City, Mich.*; and this laboratory by T. E. Glass employing a Perkin Elmer 240 Elemental Analyzer. Thin layer chromatography (tlc) was performed on Eastman 6060 precoated silica gel sheets, and spots were detected with ultraviolet light. All evaporations were carried out in vacuo.

Materials. -- Tetrahydrofuran (THF) was distilled from lithium aluminum hydride immediately before use. N,N,N',N'-Tetramethylethylene-*diamine* (TMEDA) was distilled from calcium hydride and stored over "Linde" type 3A molecular sieves. n-Butyllithium (as a solution in hexane) was obtained from Foote Mineral Company, Exton, Pa. or Ventron Corporation, Beverly, Mass. All other commercial reagents were used with-*out further purification*.

2-Hydroxy-4,6-dimethyl-5-phenylpyrimidine (1a) and 2-hydroxy-4-methyl-6-phenylpyrimidine (1b) were prepared by the method of Hauser and Manyik.[7] 2-Anilino-4-methyl-6-phenylpyrimidine (15a) was prepared by displacement of chlorine from 2-chloro-4-methyl-6-phenylpyrimidine by means of refluxing aniline and had mp 116-118°, after recrystallization from aqueous ethanol; ir ($CHCl_3$) 3400 cm^{-1} (NH); pmr ($DMSO-d_6$) δ 2.64 (s, 3, CH_3), 8.12 (m, 11, aromatic), and 10.40 (s, 1, NH).

Anal. Calcd for $C_{17}H_{15}N_3$: C, 78.13; H, 5.79; N, 16.08. Found: C, 78.03; H, 5.94; N, 15.78.

General Procedure for the Preparation and Reactions of *Dianions* 2a-b (M=Li). -- The following specific procedures involving dianion 2a (M=Li) are representative of those used to prepare other C-substituted derivatives of 1a-b via the appropriate dianions.

A. Preparation of Dianion 2a (M=Li). -- n-Butyllithium (51 ml of 1.6 M hexane solution) was added (via syringe) to a magnetically stirred suspension of 2-hydroxy-4,6-dimethyl-5-phenylpyrimidine (1a) (8.00 g, 40 mmol) and TMEDA (9.50 g, 82 mmol) in 250 ml of THF at 0° under nitrogen. After 0.5 hr, the yellow solution was assumed to contain 40 mmol of dianion 2a (M=Li).

B. Deuteration. -- Deuterium oxide (15 ml) was added to a solution of 10 mmol of 2a (M=Li) in 150 ml of THF-hexane. The two-phase mixture was extracted with two 100 ml portions of ether, which were discarded. The deuterium oxide solution was neutralized with concentrated HCl; the precipitated pyrimidine (1a) was collected, washed with 100 ml of ether, 5 ml of deuterium oxide, and then dried. Integration of the pmr spectrum ($DMSO-d_6$) of this material revealed incorporation of 0.8D into the methyl group of 1a.[13]

(13) Although neutralization of the reaction mixture with HCl may have effected some side-chain deuterium incorporation by acid-catalyzed H/D exchange, see T. J. Batterham, D. J. Brown, and H. N. Paddon-Row, J. Chem. Soc., *B*, 171 (1967), the extent of deuteration is consistent with the yields of condensation products and thus appears to provide a valid estimate of carbanion formation.

C. Benzylation. -- Benzyl chloride (5.3 g, 42 mmol), as a 50% w/v solution in THF, was added to a solution of 40 mmol of 2a (M=Li) in 250 ml of THF-hexane. The reaction was allowed to stir for 2 hr before being quenched with 150 ml of cold water. The organic phase was separated and discarded, and the aqueous phase was neutralized with 6*N* HCl. The resulting precipitate was collected, dried, and recrystallized from aqueous ethanol to afford 8.81 g (76%) of 2-hydroxy-4-methyl-5-phenyl-6-phenethylpyrimidine (3a).

D. Condensation with Benzophenone. -- Benzophenone (7.3 g, 40 mmol), as a 50% solution in THF, was added to a solution of 40 mmol of 2a (M=Li) in 250 ml of THF-hexane. After 2 hr, the reaction mixture was poured into 150 *ml of cold water. The organic phase was separated and discarded.* The aqueous phase was neutralized with 6*N* HCl to form a white precipitate, which was collected, dried, and crystallized from ethanol to give 13.5 g (69%) of 2-hydroxy-4-methyl-5-phenyl-6-(2-hydroxy-2,2-diphenylethyl)-pyrimidine (3b).

E. Condensation with Methyl Benzoate. -- A solution of methyl benzoate (1.36 g, 10 mmol) in 10 ml of THF was added dropwise to a solution of 20 mmol of 2a (M=Li) in 75 ml of THF. The reaction mixture was stirred for 2 hr before being poured into 100 ml of cold water. The organic phase was separated and discarded. The aqueous phase was neutralized with concentrated HCl to produce a yellow solid which was collected, dried, and crystallized from ethanol to afford 2.10 g (69%) of 2-hydroxy-4-methyl-5-phenyl-6-*phenacylpyrimidine* (3d).

Preparation and Reactions of Dianion 2c (M=Li). -- n-Butyllithium (75 ml of a 1.6 M hexane solution) was added to a stirred slurry of *2-hydroxy-4,6-dimethylpyrimidine hydrochloride* (1c) (6.4 g, 40 mmol) and DABCO (13.4 g, 120 mmol) in 250 ml of THF at 0° under nitrogen. After 0.5 hr., benzophenone (7.03 g, 40 mmol), as a 50% w/v solution in THF, was added. The resulting mixture was allowed to stir for 2 hr *before being poured into 50 ml of cold, dilute HCl. The resulting* precipitate was collected, washed with 100 ml of water followed by 100 ml of ether, dried, and recrystallized from ethyl acetate to afford 2.46 g (21%) of *2-hydroxy-4-methyl-6-(2-hydroxy-2,2-diphenylethyl)pyrimidine* (3m).

Similarly, condensation of 2c (M=Li) with 3,4,5-trimethoxybenzaldehyde gave pyrimidine (3n) in 10% yield.

General Procedure for the Preparation and Reactions of *Dianions* 2a-b (M=Na). -- The following specific procedures involving dianion 2b (M=Na) are representative of those used to prepare other C-substituted derivatives of 1a-b by means of sodium amide in liquid ammonia.

A. Preparation of Dianion 2b (M=Na). -- 2-Hydroxy-4-methyl-6-phenylpyrimidine (1b) (5.43 g, 30 mmol) was added to 62 mmol of sodium amide (*prepared from 62 mg-atom of sodium*) in 300 ml of liquid ammonia containing a catalytic amount of ferric nitrate. After 0.5 hr, the resulting red solution was assumed to contain 30 mmol of 2b (M=Na).

JOC-32-2

JOC-32-3

B. Benzylation. -- Benzyl chloride (4.05 g, 32 mmol), as a 50% v/v solution in anhydrous ether, was added to 30 mmol of 2b (M=Na) in 300 ml of liquid ammonia. After 2 hr, the reaction was quenched with 10 g of solid NH_4Cl, and the ammonia was evaporated (steam bath) while being replaced with *an equal volume of ether*. Addition of 150 ml of water resulted in formation of a solid at the interface, which was collected, dried, and crystallized from aqueous ethanol to afford 5.35 g (65%) of 2-hydroxy-4-phenethyl-6-phenylpyrimidine (3f).

C. Condensation with Benzophenone. -- An ethereal solution of benzophenone (5.45 g, 30 mmol) was added to 30 mmol of 2b (M=Na) in 300 ml of liquid ammonia, and the reaction mixture was stirred for 2 hr before the addition of 10 g of NH_4Cl. The ammonia was replaced with ether, and water (150 ml) was added to the ethereal suspension. The resulting solid was collected and dried to give 7.48 g (68%) of 2-hydroxy-4-phenyl-6-(2-hydroxy-2,2-diphenylethyl)pyridine (3g).

Preparation and Benzylation of Dianion 2d (M=Li). -- n-Butyllithium (26 ml of 1.6 M hexane solution) was added to a stirred suspension of 2-hydroxy-4-methyl-6-phenethylpyrimidine (3a) (5.56 g, 20 mmol) and TMEDA (4.75 g, 41 *mmol) in 250 ml of THF at 0° under nitrogen*. After 0.5 hr, the resulting brown solution was assumed to contain 20 mmol of dianion 2d (M=Li). A solution of benzyl chloride (2.70 g, 21 mmol) in 50 ml of THF was then added, and after 2 hr, the reaction was poured into 100 ml of cold water. The two-phase mixture was neutralized with 6*N* HCl, and the organic layer was separated. The aqueous layer was extracted with two 100 ml portions of ether. The combined organic extracts were dried (Na_2SO_4), and the solvent was evaporated to afford 4.33 g (57%) of 2-hydroxy-4,6-diphenethyl-5-phenylpyrimidine (3e).

Dehydration of Alcohols 3g, 3i, and 3m. -- The appropriate alcohol and a few crystals of p-toluenesulfonic acid were heated for 3-4 hr in refluxing benzene. After cooling, the crude styryl derivative was collected by filtration and dried.

Dehydration of carbinol 3g afforded, after recrystallization from ethanol, 2-hydroxy-4-phenyl-6-(2,2-diphenylethenyl)pyrimidine (5a) in 85% *yield: mp 236-238°*; ir ($CHCl_3$) 3000 (vinyl CH) and 1640 cm^{-1} (C=O); pmr ($DMSO-d_6$) δ 6.30 (s, 1, vinyl), 7.74 (m, 16, aromatic and py), and 12.50 (s, 1, NH or OH).

Anal. Calcd for $C_{24}H_{18}N_2O$: C, 82.26; H, 5.18; N, 8.00. Found: C, 82.17; H, 5.34; N, 8.25.

Dehydration of 3i gave, *after recrystallization from ethanol*, 2-hydroxy-4-phenyl-6-(4-methoxystyryl)pyrimidine (5b) in 65% *yield*: mp 273-275°; ir (KBr) 3440 (NH or OH), 3025 (vinyl CH), and 1630 cm^{-1} (C=O); pmr ($DMSO-d_6$) δ 3.96 (s, 3, OCH_3), 7.74 (m, 12, aromatic, py, and vinyl), and 12.42 (s, 1, NH or OH).

Anal. Calcd for $C_{19}H_{16}N_2O_2$: C, 74.98; H, 5.30; N, 9.20. Found: C, 75.22; H, 5.06; N, 8.95.

Similarly, dehydration of 3m afforded, after recrystallization from ethyl acetate, 2-hydroxy-4-methyl-6-(2,2-diphenylethenyl)*pyrimidine* (5c) in 44% yield; mp 244-247°; ir ($CHCl_3$) 2750 cm^{-1} (OH); pmr ($CDCl_3$) δ 2.24 (s, 3, CH_3), 5.76 (s, 1, vinyl), and 7.67 (m, 12, *aromatic, py, and OH*).

JOC-32-4

Anal. Calcd for $C_{19}H_{16}N_2O$: C, 79.14; H, 5.59; N, 9. 72. Found: C, 79.44; H, 5.75; N, 9.72.

Preparation and Benzylation of Dianion 6 (M=Li). -- n-Butylithium (51 ml of 1.6 M hexane solution) was added to a stirred suspension of 2-mercapto-4,6-*dimethylpyrimidine* (5.60 g, *40 mmol) in 250 ml of THF* at 0° under nitrogen. The resulting brown suspension was stirred for 0.5 hr before the addition of a solution of benzyl chloride (5.30 g, 42 mmol) in 50 ml of THF. After 3.5 hr, the reaction mixture was poured into 150 ml of cold water, and *the layers were separated*. The aqueous layer was washed with 100 ml of ether, and the combined organic extracts were discarded. The aqueous solution was neutralized with concentrated HCl. Tlc of the resulting oil indicated the presence of four products; while pmr analysis ($DMSO-d_6$) revealed the presence of S-benzylated products as evidenced by resonances at 4.26, 4.32, and 4.37 ppm characteristic of methylene adsorption of aromatic benzyl sulfides. Upon standing at 0°, the oil crystallized to afford 2.63 g (29%) of 2-mercapto-4-methyl-6-phenethylpyrimidine (7), which was recrystallized from ethanol: mp 165-166°; pmr ($DMSO-d_6$) δ 2.14 (s, 3, CH_3), 2.76 (s, 4, CH_2), 5.56 (s, 1, py), and 7.10 (s, 5, aromatic).

Anal. Calcd for $C_{13}H_{14}N_2S$: C, 67.83; H, 6.09; N, 12.17. Found: C, 68.13, H, 5.97; N, 11.89.

Benzylation of the Dilithio Salts of 2,6-Dimethyl-4-hydroxypyrimidine (8). -- *n-Butyllithium (11.05 ml of 1.9M hexane solution was added to a* stirred solution of 2,6-dimethyl-4-hydroxypyrimidine (1.24 g, 10 mmol) in 125 ml of THF at 0° under nitrogen, and the resulting yellow suspension was stirred for 1 hr before the addition of benzyl chloride (1.39 g, 11 *mmol). After 2.5 hr, the reaction solution was poured into 100 ml of* iced water, and the two-phase mixture was neutralized with concentrated HCl. The organic phase was separated, and the aqueous phase was extracted with two 100 ml portions of ether. The combined organic extracts were dried ($MgSO_4$), and the solvent was evaporated. *The resulting yellow oil* was chromatographed on silica gel. Elution with benzene-acetone gave initially, 0.21 g(7%) of 2,6-diphenethyl-4-hydroxypyrimidine (10c), mp 158-161°, after recrystallization from acetone-hexane. Additional recrystallizations raised the mp to 161.5-163°: ir ($CHCl_3$) 3040 (NH) and 1645 cm^{-1} (C=O); pmr ($DMSO-d_6$) δ 2.76 (m, 8, CH_2), 5.94 (s, 1, py), and 7.10 (s, 10, aromatic).

Anal. Calcd for $C_{20}H_{20}N_2O$: C, 78.91; H, 6.62; N, 9.21. Found: C, 78.69; H, 6.33; N, 9.05.

Continued elution with benzene-acetone afforded 0.26 g (13%) of *2-phenethyl-4-hydroxy-6-methylpyrimidine* (10b), mp 160-165° after recrystallization from acetone-hexane. Two additional recrystallizations gave analytically pure material, mp 166-167°: ir (KBr) 1655 cm^{-1} (C=O); pmr ($DMSO-d_6$) δ 2.12 (s, 3, CH_3), 2.82 (m, 4, CH_2), 5.96 (s, 1, py), and *7.16 (s, 5, aromatic)*.

Anal. Calcd for $C_{13}H_{14}N_2O$: C, 72.87; H, 6.59; N, 13.08. Found: C, 73.04; H, 6.84; N, 13.13.

JOC-32-5

*Further elution with benzene-acetone gave 1.02 g (48%) of 2-methyl-*4-hydroxy-6-phenethylpyrimidine (10a), *mp 125.5-127° after recrystallization* from acetone-hexane: ir ($CHCl_3$) 1655 cm^{-1} (C=O); pmr ($DMSO-d_6$) δ 2.22 (s, 3, CH_3), 2.72 (m, 4, CH_2), 5.88 (s, 1, py), and 7.12 (s, 5, aromatic).

Anal. Calcd for $C_{13}H_{14}N_2O$: C, 72.87; H, 6.59; N, 13.08. Found: C, 73.17; H, 6.62; N, 13.25.

Benzylation of 2,6-Dimethyl-4-hydroxypyrimidine in the Presence of 3 Equiv of n-Butyllithium. -- n-Butyllithium (5.80 ml of 1.9*M* hexane solution) was added to a solution of 2,6-dimethyl-4-hydroxypyrimidine (8) (0.62 g, 5 mmol) in 50 ml of THF at 0° under nitrogen. After 0.5 hr, *a solution of TMEDA (0.64 g, 5.5 mmol) in 25 ml of THF was added, followed* by n-butyllithium (3.90 ml of 1.9*M* hexane solution). The resulting yellow-orange slurry was stirred for 1.5 hr before the addition of benzyl chloride (1.46 g, 11.5 mmol). After 2 hr, the reaction solution was *poured into 50 ml of iced water, and the aqueous mixture was neutralized* with concentrated HCl. The organic phase was separated, and the aqueous phase was extracted with two 50 ml portions of ether. The combined organic extracts were dried ($MgSO_4$), and the solvent was evaporated. Chromatography of the *resulting oil (eluting with benzene-acetone) afforded* 0.26 g (17%) of 10c, 0.04 g (4%) of 10b, and 0.35 g (33%) of 10a.

Butylation of the Dilithio Salts of 2,6-Dimethyl-4-hydroxypyrimidine (8). -- *A solution of 1-bromobutane (3.01 g, 22 mmol) in 25 ml of THF* was added dropwise to a stirred slurry of 20 mmol of the dilithio salt of 8 (prepared as described in the previous experiment) in 200 ml of THF-hexane at 0° under nitrogen. After 2 hr, the reaction solution was poured into 100 ml of iced water, and the aqueous mixture was neutralized with concentrated HCl. The organic phase was separated and the aqueous phase was extracted with two 100 ml portions of ether. The combined organic extracts were dried ($MgSO_4$), and the solvent was evaporated. The resulting brown oil was chromatographed on silica gel. Elution with ether-hexane gave, initially, 0.37 g (8%) of 2,6-dipentyl-4-hydroxypyrimidine (11c) as an oil, bp 182-185° (1 mm): ir (film) 1675 cm^{-1} (C=O); pmr ($DMSO-d_6$) δ 0.80 (t, 6, CH_3), 1.20 (m, 8, CH_2), 1.52 (m, 4, CH_2), 2.32 (m, 4, CH_2), and 5.82 (s, 1, py).

Anal. Calcd for $C_{14}H_{24}N_2O$: C, 71.14; H, 10.24; N, 11.85. Found: C, 71.16; H, 10.44; N, 11.63.

Continued elution with ether-hexane afforded 0.65 g (18%) of 4-hydroxy-6-methyl-2-pentylpyrimidine (11b), mp 79-81° after two recrystallizations from pentane (lit.[14] mp 80-81°); pmr ($DMSO-d_6$) δ 0.84 (t, 3, CH_3), 1.30 (m, 4, CH_2), 1.67 (m, 2, CH_2), 2.16 (s, 3, CH_3), 2.52 (t, 2, CH_2), and 5.97 (s, 1, py).

(14) G. W. Miller and F. L. Rose, J. Chem. Soc., 5492 (1963).

JOC-32-6

Further elution with ether-hexane gave 1.41 g (39%) of 4-hydroxy-*2-methyl-6-pentylpyrimidine* (11c), *mp 87-88.5°* after recrystallization from petroleum ether: ir ($CHCl_3$) 1655 cm^{-1} (C=O); pmr ($DMSO-d_6$) δ 0.82 (t, 3, CH_3), 1.22 (m, 4, CH_2), 1.48 (m, 2, CH_2), 2.16 (s, 3, CH_3), 2.31 (t, 2, CH_2), and 5.86 (s, 1, py).

Anal. Calcd for $C_{10}H_{16}N_2O$: C, 66.64; H, 8.95; N, 15.54. Found: C, 66.77; H, 9.01; N, 15.62.

Preparations and Reactions of Dianion 12. -- n-Butyllithium (11.1 ml of a 1.89 *M* hexane solution) was added to a stirred solution of 2-methyl-4(3H)-quinazolinone (1.60 g, 10 mmol) in 125 ml of THF at 0° under *nitrogen. After 1 hr, the deep red solution was assumed to contain 10* mmol of dianion 12. A solution of the appropriate electrophile in 25 ml THF was then added dropwise. After 2 hr, the reaction mixture was poured into 100 ml of iced water, and the aqueous mixture was neutralized with concentrated HCl. The organic layer was separated, and the aqueous layer was extracted with two 100 ml portions of ether. The organic extracts were dried (Na_2SO_4), and the solvent was evaporated. Recrystallization of the crude products from appropriate solvents afforded 13a-e (Table I). Although the mp of 13b was somewhat lower *than that reported by earlier investigators, the pmr spectrum of our* material was completely consistent with the assigned structure: pmr ($DMSO-d_6$) δ 0.93 (t, 3, CH_3), 1.76 (m, 2, CH_2), 2.59 (t, 2, CH_2), and *7.76* (m, 4, aromatic).

Dehydration of Carbinol 13d. -- The alcohol (0.50 g, 1.46 mmol) was stirred in 25 ml of aqueous H_2SO_4 (3:2) for 2.5 hr at room temperature. The reaction mixture was poured into 100 ml of iced water and made alkaline with concentrated NH_4OH. The aqueous mixture was extracted with two 25 ml portions of chloroform. The organic solution was dried ($MgSO_4$), and the solvent was evaporated to give a light yellow solid. Recrystallization from ethyl acetate gave 0.37 g (79%) of 2-(2,2-diphenyl-ethenyl)-4(3H)-quinazolinone (13f), mp 207-208°; pmr ($DMSO-d_6$) δ 6.83 (s, 1, vinyl), 7.41 (m, 13, aromatic), and 8.03 (d, 2, aromatic).

Anal. Calcd for $C_{22}H_{16}N_2O$: C, 81.64; H, 4.97; N, 8.64. Found: C, 81.96; H, 5.16; N, 8.93.

Preparation and Reactions of Dianion 16a (M=Li). -- n-Butyllithium (37.5 ml of 1.6 M hexane solution) was added (via syringe) to a stirred solution of 2-anilino-4-methyl-6-phenylpyrimidine (15a) (7.85 g, 30 mmol) in 150 ml of THF at 0° under nitrogen. After 0.5 hr, the deep red solution was assumed to contain 30 mmol of dianion 16a (M=Li).

A. Deuteration. -- A solution of 16a (M=Li) was quenched with 15 ml of *deuterium oxide. After stirring for 0.5 hr, the layers were separated*, and the deuterium oxide solution was extracted with two 100 ml portions of ether. The combined organic extracts were dried (Na_2SO_4), and the solvent was evaporated to give deuterated 15a. Pmr analysis ($DMSO-d_6$) disclosed incorporation of *0.81D per methyl group*.

B. Benzylation. -- Benzyl chloride (2.78 g, 22 mmol), as a 50% v/v solution in THF, was added to a stirred solution of 20 mmol of 16a (M=Li) in THF-hexane. After 2 hr, the reaction was quenched by the addition of 50 ml of cold, dilute HCl. The precipitate which formed was collected and neutralized with dilute NH_4OH. The resulting aqueous solution, containing an oil, was extracted with three 100 ml portions of ether. The ethereal extracts were dried (Na_2SO_4), and the solvent was evaporated to give an oil which crystallized on standing. Recrystallization from aqueous ethanol gave 4.70 g (70%) of 2-anilino-4-phenyl-6-phenethyl-pyrimidine (17a).

JOC-32-7

C. Condensation with Benzophenone. -- Benzophenone (4.00 g, 22 mmol), as a 50% w/v solution in THF, was added to a stirred solution of 20 mmol of 16a (M=Li) in THF-hexane, and the mixture was allowed to stir for 2 hr. The reaction mixture *was poured into 100 ml of cold, dilute HCl*. The resulting yellow precipitate was collected, washed with 100 ml of 5% $NaHCO_3$ followed by 100 ml of water, and then dried. Recrystallization from ethanol gave 7.81 g (90%) of 2-anilino-4-phenyl-6-(2-hydroxy-2,2-diphenylethyl)pyrimidine (17b).

D. Condensation with 3,4-Dichloro-4'-trifluoromethylbenzophenone. -- A 50% v/v solution of 3,4-dichloro-4'-trifluoromethylbenzophenone (11.24 g, 32 mmol) in THF was added to 30 mmol of 16a (M=Li) in THF-hexane, and *the reaction was stirred for 2 hr. The mixture was poured into 100 ml* of cold, dilute HCl, and the crude hydrochloride salt was collected and then neutralized with dilute NH_4OH. The free base was extracted into ether and the resulting ethereal solution was saturated with gaseous *HCl to give a precipitate which was collected and dried. Crystallization* from aqueous ethanol afforded 16.23 g (85%) of 2-anilino-5-phenyl-6-[2-hydroxy-2-(4-trifluoromethylphenyl)-2-(3,4-dichlorophenyl)ethyl]-pyrimidine hydrochloride (17c).

E. Condensation with Cyclohexanone. -- A solution of cyclohexanone (3.12 g, 32 mmol) in 10 ml of THF was added to 30 mmol of 16a (M=Li). After 2 hr, the reaction mixture was poured into 150 ml of cold water; the layers were separated, and the aqueous layer was extracted with three 100 ml portions of ether. The combined organic extracts were dried (Na_2SO_4), and the solvent was evaporated to give an oil which crystallized on standing. Recrystallization from aqueous ethanol afforded *5.92 g (53%) of 2-anilino-4-phenyl-6-(1-hydroxycyclohexylmethyl)-*pyrimidine (17d).

F. Condensation with Anisaldehyde. -- A 50% v/v solution of anisaldehyde (3.00 g, 22 mmol) in THF was added to 20 mmol of 16a (M=Li) in THF-hexane. After 2 hr, the reaction was poured into 50 ml of cold, dilute HCl; the resulting precipitate was collected, washed with water, dilute NH_4OH, and water once again. Crystallization from ethanol gave 6.20 g (80%) of 2-anilino-4-phenyl-6-[2-hydroxy-2-(4-methoxyphenyl)ethyl]pyrimidine (17e).

G. Condensation with Heptaldehyde. -- Heptaldehyde (2.51 g, 22 mmol), as a 50% v/v solution in THF, was added to 20 mmol of 16a (M=Li), and *the resulting mixture was stirred for 2 hr before being hydrolyzed with* 150 ml of cold water. The layers were separated, and the aqueous layer was extracted with two 100 ml portions of ether. The combined organic extracts were dried ($MgSO_4$), and the solvent was removed. The resulting *oil was dissolved in 200 ml of ether, and the ethereal solution was* saturated with gaseous HCl. The resulting precipitate was collected and recrystallized from ethyl acetate to provide 3.28 g (40% of 2-anilino-4-phenyl-6-(2-hydroxyoctyl)pyrimidine hydrochloride (17f).

JOC-32-8

Condensation of Dianion 16a (M=Na) with Benzophenone. -- 2-Anilino-4-methyl-6-phenyl-pyrimidine (15a) (5.32 g, 20 mmol) was added to a *stirred suspension of 40 mmol of sodium amide* (prepared from 40 mg-atom of sodium) in 300 ml of liquid ammonia. After, 0.5 hr, the deep red solution was assumed to contain 20 mmol of dianion 16a (M=Na). Benzophenone (3.64 g, 20 mmol) was then added. The mixture was allowed to *stir for 2 hr before the addition of 10 g of solid* NH_4Cl. The ammonia was evaporated while being replaced with an equal volume of ether, and then 100 ml of water was added. The layers were separated and the aqueous layer was extracted with two 100 ml *portions of ether. The combined ethereal extracts were dried* (Na_2SO_4), and the solvent was evaporated to give an oil which crystallized slowly. Recrystallization from ethanol gave 3.32 g (38%) of 17b.

Benzylation of 15b in the Presence of 2 Mol Equiv of Sodium Amide. -- 2-Amino-4-methylpyrimidine (15b) (3.29 g, 30 mmol) was added to a stirred suspension of 62 mmol of sodium amide (prepared from 62 mg-atom of sodium) in 300 ml of liquid ammonia. After the light green solution had been stirred for 0.5 hr, benzyl chloride (4.05 g, 32 mmol), as a 50% v/v solution in anhydrous ether, was added. This addition caused the reaction mixture to lose the characteristic purple color associated with stilbene formation.[15] After 1 hr, the reaction was quenched by the *addition of 10 g of solid* NH_4Cl. Replacement of the ammonia by an equal volume of ether followed by addition of 100 ml of water caused the formation of a solid at the interface. The solid was collected, dried, and crystallized from ethanol to give 0.64 g (11%) of 2-amino-4-phenethylpyrimidine (17g), mp 162-164° (lit.[15] mp 162-164°). After removal of 17g by filtration, the ethereal layer was separated and dried (Na_2SO_4). Removal of the solvent and recrystallization *of the resulting solid from ethanol afforded 1.04 g (61%) of stilbene*, mp 122-124° (lit.[16] mp 124°).

(15) T. Matsukawa and K. Shirakawa, J. Pharm. Soc. Japan, 72, 909 (1952).

(16) *T. W. J. Taylor and A. R. Murray, J. Chem. Soc., 2079 (1938).*

Benzylation of 15b in the Presence of 2 Mol Equiv of n-Butyllithium. -- n-Butyllithium (16.6 ml of a 1.9 M hexane solution) was added to a solu*tion of 15b (1.84 g, 15 mmol) in 75 ml of THF at 0° under nitrogen, and* the yellow-orange solution was stirred for 0.75 hr before the addition of benzyl chloride (1.86 g, 15 mmol). After 2 hr, the reaction mixture was poured into 75 ml *of cold water and neutralized* with concentrated *HCl. The organic layer was separated, and the aqueous layer was extracted* with two 50 ml portions of ether. The organic extracts were dried ($MgSO_4$), and the solvent was evaporated. Recrystallization of the resulting solid from ethanol afforded 0.14 g (5%) of 17g, mp 157-159°, mmp 157-160° (lit.[16] mp 162-164°).

JOC-32-9

Benzylation of 15b in the Presence of 2 Mol Equiv of n-Butyllithium-TMEDA Complex. -- n-Butyllithium (51.3 ml of 1.6 M hexane solution) *was added to a solution of 15b (4.36 g, 40 mmol) and TMEDA (9.51 g,* 82 mmol) in 200 ml of THF at 0° under nitrogen. After 0.5 hr, benzyl chloride (5.30 g, 42 mmol), as a 50% v/v solution in THF, was added. The reaction mixture was allowed to stir 2 hr and was then worked up as *in the preceeding experiment. Recrystallization from ethanol gave 2.83 g* (36%) of phenethyl derivative 17g, mp 162-164°.

Benzylation of 15b in the Presence of 3 Mol Equiv of n-Butyllithium. -- n-Butyllithium (51 ml of 1.6 M hexane solution) was added to a solution of 15b (4.36 g, 40 mmol) in 150 ml of THF at 0° under nitrogen. After 0.5 hr, benzyl chloride (5.30 g, 42 mmol) was added as an 0% v/v solution in THF. Workup of the reaction mixture after 2 hr afforded material whose pmr spectra possessed a methylene envelope, characteristic of a n-butyl group, at 0.72-1.68 ppm. Recrystallization of this material gave 1.87 g (24%) of 17g, mp 162-164°.

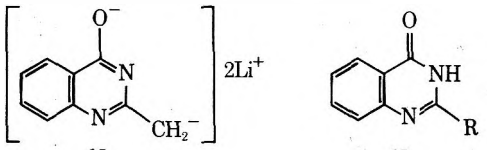
Preparation and Reactions of Dianion 16b (M=Li) Employing 3 Mol Equiv of n-Butyllithium-TMEDA Complex. -- n-Butyllithium (76 ml of a 1.6 M hexane solution) was added to a solution of 15b (4.36 g, 40 mmol) and TMEDA (9.51 g, 120 mmol) in 200 ml of THF at 0° under nitrogen, and *the reaction mixture was stirred for 0.5 hr*. The appropriate electrophile was added as a solution in THF, and the resulting reaction solution was stirred for 2 hr before workup.

Reactions of 16b (M=Li) with benzyl chloride, cyclohexanone, piperonal, *and heptaldehyde were quenched by pouring into 100-200 ml of cold water*. The products 17g and 17i-k were isolated by filtration or by extraction with ether, and then recrystallized from the appropriate solvent (Table I).

The condensation product of 16b (M=Li) with benzophenone was obtained by pouring the reaction mixture into 100 ml of cold dilute HCl, collection of the resulting mixture of HCl salts, washing with dilute NH_4OH, and drying. *Recrystallization from aqueous ethanol afforded* 17h.

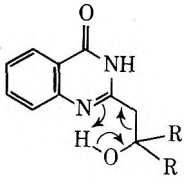
Deuteration was accomplished by adding 0.5 ml of deuterium oxide to a solution of 5 mmol of 16b (M=Li) in THF. After 5 min, the resulting slurry was filtered to remove the precipitated lithium deuteroxide. The filtrate was diluted with 100 ml of ether, dried ($MgSO_4$), concentrated, and the resulting deuterated product was dried overnight in vacuo. Pmr analysis ($DMSO-d_6$) of this material revealed incorporation of 0.76D/methyl group and 0.67D/amino group of 15b.

in selective modification of the original methyl group to form **13a–e** (Table I). These reactions apparently represent the first examples of a direct, general method for side-chain elaboration of 2-alkyl-4(3*H*)-quinazolinones.[9]



12 **13**

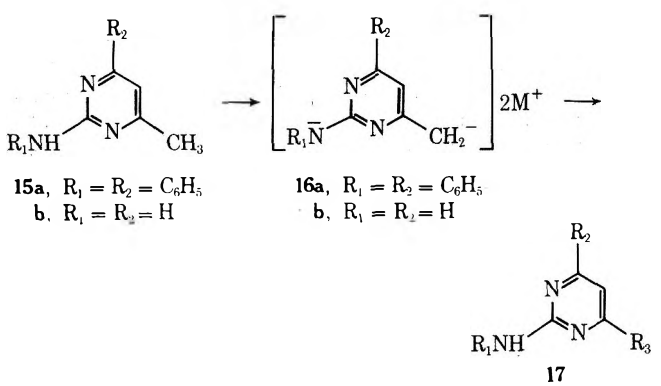
It should be noted that attempts to effect either thermal or PTSA-catalyzed dehydration of carbinols **13c** and **13d** resulted only in retroaldol reactions. Such lability is attributed to the fact that these compounds exist largely as the lactam tautomers (**14**) where the strategically positioned sp^2 ring nitrogen acts as an intramolecular catalytic center for retrocondensation.[10] However, dehydration of **13d** to form **13f** [R = CH=C(C_6H_5)$_2$], without concurrent retroaldol reaction, could be realized by means of aqueous sulfuric acid. In this more acidic medium, protonation of the ring nitrogen may prevent intramolecular degradation of **13d**, thereby allowing the normal mode of dehydration to become the major course of reaction.



14

Turning next to several representative 2-amino-4-methylpyrimidines, it was found that 2-anilino-4-methyl-6-phenylpyrimidine (**15a**) underwent smooth twofold metalation with *n*-butyllithium complexed with TMEDA or sodium amide in liquid ammonia to yield dianion **16a** (M = Li or Na). Reactions of these dialkali salts with a representative series of electrophiles afforded methyl-substituted derivatives **17a–f** in good yields (Table I).

Conversion of 2-amino-4-methylpyrimidine (**15b**) into dianion **16b** (M = Na) by means of sodium amide in liquid ammonia was incomplete, as evidenced by stilbene formation[11] upon addition of benzyl chloride; the expected C-alkyl derivative **17g** was isolated in only 11% yield. Reactions of **15b** with *n*-butyllithium were characterized by some rather unexpected stoichiometry. Thus, treatment of **15b** with 2 equiv of the alkyllithium reagent, followed by benzyl chloride, afforded only a 5% yield of phenethyl derivative **17g**. Complexation of the organolithium reagent (2 equiv) with TMEDA effected an increase in metalation of the 4-methyl group as shown by the formation of **17g** in 36% yield upon addition of benzyl chloride. When 3 equiv of uncomplexed *n*-butyllithium was employed, the yield of **17g** was lowered to 24% owing to competition between metalation at the 4-methyl group and addition of the alkyllithium to the azomethine linkage. Subsequently it was found that 3 equiv of *n*-butyllithium–TMEDA complex effected metalation of the 4-methyl group of **15b** to an extent satisfactory for synthetically useful condensations with electrophiles. For example, deuteration produced **15b** containing 0.74 D/methyl group, while alkylation with benzyl chloride afforded **17g** in 58% yield. Similarly, reactions with benzophenone, cyclohexanone, piperonal, and heptaldehyde gave the anticipated products **17h–k** (Table I). Although we suspected that the metalated species involved in these reactions might be the trilithio salt resulting from abstraction of both amino protons and a methyl hydrogen from **15b**,[12] this premise was negated by the absence of N-alkylated products and by the finding that deuterium oxide quenches failed to incorporate more than one deuterium at the 2-amino group of **15b**. It is therefore assumed that the major reactive intermediate in the observed condensations employing 3 equiv of alkyllithium–TMEDA complex is dianion **16b** (M = Li).



15a, $R_1 = R_2 = C_6H_5$; **b**, $R_1 = R_2 = H$ **16a**, $R_1 = R_2 = C_6H_5$; **b**, $R_1 = R_2 = H$

17

In conclusion, it should be pointed out that the present dianion approach to pyrimidine structure modification offers a facile new route to numerous hydroxy- and aminopyrimidines from readily available starting materials without requiring construction of the heterocyclic ring from acyclic precursors.[2] In the interest of experimental convenience and ease of dianion formation the use of *n*-butyllithium to sodium amide as the metalating agent is preferred.

Registry No.—**1a**, 50324-02-2; **1b**, 6320-47-4; **1c** HCl, 34289-60-6; **2a** (Li), 50324-05-5; **2a** (Na), 50324-06-6; **2b** (Li), 50324-07-7; **2b** (Na), 50324-08-8; **2c** (Li), 50324-09-9; **2d** (Li), 50324-10-2; **3a**, 27433-90-5; **3b**, 27433-89-2; **3c**, 50324-13-5; **3d**, 50324-14-6; **3e**, 50324-15-7; **3f**, 27433-91-6; **3g**, 50324-17-9; **3h**, 27433-92-7; **3i**, 50324-19-1; **3j**, 50324-20-4; **3k**, 50324-21-5; **3l**, 50324-22-6; **3m**, 50324-23-7; **3n**, 50324-24-8; **5a**, 27433-93-8; **5b**, 50324-26-0; **5c**, 50324-27-1; **6** (Li), 50324-28-2; **7**, 50324-29-3; **8**, 6622-92-0; **9a**, 50324-31-7; **9b**, 50324-32-8; **10a**, 50324-33-9; **10b**, 50324-34-0; **10c**, 50324-35-1; **11a**, 50324-36-2; **11b**, 50324-37-3; **11c**, 50324-38-4; **12** (Li), 50324-39-5; **13a**, 4765-57-5; **13b**, 4765-54-2; **13c**, 50324-42-0; **13d**, 50324-43-1; **13e**, 50324-44-2; **13f**, 50324-45-3; **15a**, 50324-46-4; **15b**, 108-52-1; **16a** (Li), 50324-48-6; **16a** (Na), 50324-49-7; **16b** (Li), 50324-50-0; **16b** (Na), 50324-51-1; **17a**, 50324-52-2; **17b**, 50324-53-3; **17c** HCl, 50324-54-4; **17d**, 50324-55-5; **17e**, 50324-56-6; **17f** HCl, 50324-57-7; **17g**, 50324-58-8; **17h**, 50324-59-9; **17i**, 50324-60-2; **17j**, 50324-61-3; **17k**, 50324-62-4; benzyl chloride, 100-44-7; benzophenone, 119-61-9; cyclohexanone, 108-94-1; methyl benzoate, 93-58-3; anisaldehyde, 123-11-5; heptaldehyde, 111-71-7; ethyl acetate, 141-78-6; 3,4,5-trimethoxybenzaldehyde, 86-81-7; ethyl bromide, 74-96-4; acetophenone, 98-86-2; 3,4-dichloro-4′-trifluoromethylbenzophenone, 34328-34-2; piperonal, 120-57-0; 2-chloro-4-methyl-6-phenylpyrimidine, 32785-40-3; 2-mercapto-4,6-dimethylpyrimidine, 13139-97-4; 2-methyl-4(3*H*)-quinazolinone, 1769-24-0.

Supplementary and Miniprint Material Available. Analytical and pmr spectral data for all new compounds will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material and full-sized photocopies of the miniprinted material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the miniprinted and supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N. W., Washington, D. C. 20036. Remit check or money order for $4.00 for photocopy or $2.00 for microfiche, referring to code number JOC-74-595.

References and Notes

† This paper contains "miniprint." See Editorial regarding miniprint on p 8A of the Jan 11, 1974, issue.

(1) (a) For part IV of this series, see J. V. Hay, D. E. Portlock, and J. F. Wolfe, *J. Org. Chem.*, **38**, 4379 (1973). (b) A preliminary account of a portion of the present work has appeared: J. F. Wohe and T. P. Murray, *J. Chem. Soc., Chem. Commun.*, 1040 (1970). (c) This investigation was supported by Grants GM-14340 and NS-10197 from the National Institutes of Health and by Contract No. DA-49-193-MD-3024 from the U. S. Army Research and Development Command.

(2) See (a) D. J. Brown in "The Chemistry of Heterocyclic Compounds," A. Weissberger, Ed., Interscience, New York, N. Y., 1962. (b) D. J. Brown in "The Chemistry of Heterocyclic Compounds," A. Weissberger, Ed., Interscience, New York, N. Y., 1970, Supplement I.
(3) R. S. Klein and J. J. Fox, *J. Org. Chem.*, **37**, 4381 (1972).
(4) C. R. Hauser and R. M. Manyik, *J. Org. Chem.*, **18**, 588 (1953).
(5) (a) T. D. Heys and J. C. Roberts, *J. Chem. Soc.*, 328 (1951); (b) J. C. Roberts, *ibid.*, 3065 (1952).
(6) (a) A. W. Langer, Jr., *Trans. N. Y. Acad. Sci.*, **27**, 741 (1965); (b) M. D. Raush and D. J. Ciappenelli, *J. Organometal. Chem.*, **10**, 127 (1967).
(7) (a) W. A. Butte, *J. Org. Chem.*, **29**, 2928 (1964); (b) E. J. Corey and D. Seebach, *ibid.*, **31**, 4097 (1966).
(8) 2,4,6-Trimethylpyrimidine has been shown to undergo metalation with phenyllithium exclusively at the 4-methyl group.[6]
(9) (a) 2-Methyl-4(3*H*)-quinazolinone has been shown to undergo condensation at the methyl group with chloral: P. Y. Kulkarni, *J. Indian Chem. Soc.*, **19**, 180 (1942). (b) The *N*-phenyl derivative also has been reported to undergo similar reactions with other aldehydes: B. D. Singh and D. N. Chaudbury, *ibid.*, **45**, 311 (1968). (c) Alkylation of 2-methyl-4(3*H*)-quinazolinone employing sodium hydride reportedly gives only N- and O-alkylated products: C. Bogentoft, L. Kronberg, and B. Danielsson, *Acta Pharm. Suecica*, **6**, 489 (1969).
(10) A. I. Meyers, A. Nabeya, H. W. Adickes, I. R. Politzer, G. R. Malone, A. G. Kovelesky, R. L. Nolen, and R. C. Portnoy, *J. Org. Chem.*, **38**, 36 (1973).
(11) See R. L. Gay and C. R. Hauser, *J. Amer. Chem. Soc.*, **89**, 1647 (1967), and references cited therein.
(12) Related 1,1-dianions derived from aromatic, primary amines and 1,1-diarylhydrazines have recently been reported: R. West and H. F. Stewart, *J. Amer. Chem. Soc.*, **92**, 853 (1970).

Metallo Aldimines. A Masked Acyl Carbanion[1,2]

G. E. Niznik, W. H. Morrison, III, and H. M. Walborsky*

Department of Chemistry, Florida State University, Tallahassee, Florida 32306

Received September 10, 1973

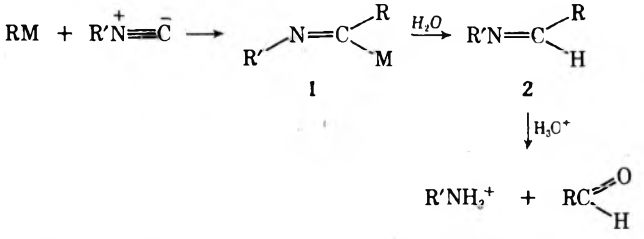
The addition of lithium and Grignard reagents to isocyanides not containing α hydrogens proceeds by an α addition to produce metallo aldimines. The lithium aldimines are versatile reagents which can be used as precursors for the preparation of aldehydes, ketones, α diketones, α-hydroxy ketones, α-keto acids, α- and β-hydroxy acids, and silyl ketones.

There has been a paucity of work on the reaction of organolithium and Grignard reagents with isocyanides. In 1904 Sachs and Loevy[3] added phenylmagnesium bromide to methyl isocyanide and detected benzaldehyde from the steam distillate. Gilman and Heckert[4] 24 years later verified this reaction and reported isolating a 2.5% yield of benzaldehyde; however, the use of ethyl isocyanide or *tert*-butyl isocyanide proved unsuccessful. In 1961, another attempt to use this reaction was made by Ugi,[5] who showed, under a variety of conditions, that the reaction of phenylmagnesium bromide with cyclohexyl isocyanide gave only a 1.5% yield of benzaldehyde.

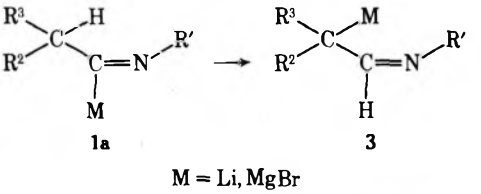
The recent discovery in our laboratory that organolithium reagents added to isocyanides[6] prompted a reinvestigation of this problem. This paper deals with the α addition of organolithium and Grignard reagents to isocyanides to yield metallo aldimines (1) and the use of these metallo aldimines as precursors for the synthesis of a variety of functional groups.

Results and Discussion

1-Metallo Aldimines. Metallo aldimines can be most simply prepared by the α addition of an organometallic reagent to an appropriate isocyanide.



That metallo aldimine 1 is an intermediate is inferred from the fact that addition of water to 1 yields the aldimine 2, which can be isolated. Hydrolysis of 1 or 2 produces the corresponding aldehyde and amine salt. To resolve the question of whether 1 rearranges to give 3, the metallo aldimine was quenched with D_2O (>99%) and then hydrolyzed. The deuterioaldehyde formed was shown by nmr analysis to have greater than 98% deuterium in the 1 position, which confirms the structural assignment as 1.



M = Li, MgBr

However, during the deuterolysis of various halomagnesium aldimines, it was observed that less than 100% of the deuterium was incorporated into the C-1 position, and incorporation of some deuterium occurred at the C-2 position (Table III). Several explanations could be conjectured for the presence of deuterium at C-2. First, addition of Grignard reagents to isocyanides requires several hours at room temperature, in contrast to the rapid addition of lithium reagents, and the long reaction time may permit rearrangement of **1a** to the more thermodynamically stable **3**. Secondly, the metallo aldimine **1a** could abstract a proton from the ether solvent and finally a C-2 hydrogen could be abstracted by **1a** during deuterolysis.

To determine if the lithium aldimine was stable to rearrangement, two experiments were conducted. In the first experiment, ethyllithium was added to 1,1,3,3-tetramethylbutyl isocyanide (TMBI) in diethyl ether at 0°. The mixture was stirred for 75 min, then quenched with a fivefold excess of D_2O. The aldimine was distilled, and from the nmr spectrum the relative deuterium content at C-1 and C-2 positions was determined (the methylene protons of the 1,1,3,3-tetramethylbutyl moiety at 1.51 ppm were used as an internal standard). Only 86% incorporation of the deuterium occurred at C-1 while 14% occurred at C-2. The observation that 100% of the deuterium was incorporated into the aldimine suggests[7] that **1a** is not abstracting a proton from the ether solvent, since if this were the case less than 100% deuterium would be incorporated.

The other experiment that was performed involved the addition of ethyllithium to TMBI in ether followed by stirring the reaction mixture at 0° for 6 hr. An inverse ad-

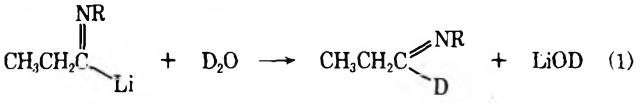
Table I
Synthesis of Aldimines and Aldehydes from the α Addition of Organolithiums to Isocyanides

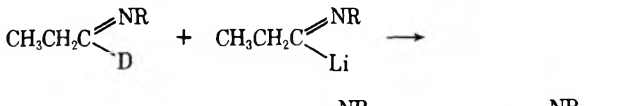
Registry no.	RLi	Solvent	Isonitrile (registry no.)	% aldimine (registry no.)	Overall % aldehyde[c] (purity, %) (registry no.)
109-72-8	*n*-Butyl	Pentane	TMBI (14542-93-9)	100[a] (49707-47-3)	
59830-1	*sec*-Butyl	Pentane	TMBI	100[a] (49707-48-4)	
	n-Butyl	Ether	TMBI		93[b] (92) (110-62-3)
	sec-Butyl	Ether	TMBI		96[b] (94) (96-17-3)
594-19-4	*tert*-Butyl	Ether	TMBI	93 (49707-49-5)	92 (630-19-3)
	n-Butyl	Ether	TBI[d] (7188-38-7)	92[e] (49707-50-8)	
811-49-4	Ethyl	Ether	DMPI[f] (2769-71-3)	50[g] (49707-51-9)	
591-51-5	Phenyl	Ether	TMBI	45–67[g] (49707-52-0)	55[b] (87) (100-52-7)
917-57-7	Vinyl	Ether	TMBI	0	
	Phenylethynyl	Ether	TMBI	0	
	sec-Butyl	Ether	TMBI	93[h,i] (34668-70-7)	92[b,i] (98.6) (25132-57-4)

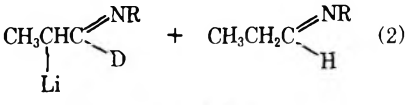
[a] Analytically pure crude product. [b] Purities were determined by vpc analysis. [c] Beilstein, "Handbuch der organische Chemie, Dritte Teil," Friedrich Richter, Springer-Verlag, Berlin, 1959. [d] *tert*-Butyl isocyanide. [e] Crude yield, 90% pure. [f] 2,6-Dimethylphenyl isocyanide. [g] Yields based on nmr analysis of crude product. [h] Yield recovered after distillation. [i] *1-d* compound.

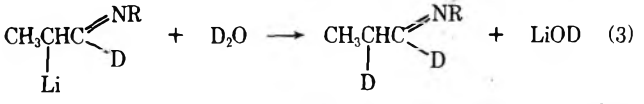
dition was carried out in which the reaction mixture was transferred under anhydrous conditions to a stirred flask containing a fivefold excess of D_2O in THF at −15°. The deuterium analysis showed 97% deuterium incorporation at C-1 and only 3% at C-2.

From the analysis it was clear that **1a** was not being converted to **3** to any appreciable extent, since only 3% was converted in this manner over a 6-hr period (usually the reaction is run for 15–30 min). It is concluded that deuterolysis at C-2 is occurring during the addition of D_2O to the lithium aldimine as shown in eq 1–3. It is suggested


(1)



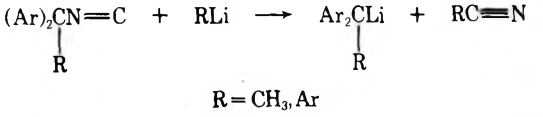

(2)


(3)

that to avoid this side reaction, reactions of metallo aldimines should be performed by the addition of the metallo aldimine to the substrate.

In summary, it can be stated that the 1-lithio aldimine is stable in solution and exists as structure **1a**. It should be noted that in contrast to the above, the reaction of *sec*-butyllithium with TMBI followed by the addition of D_2O to the reaction mixture resulted in incorporation of 97% deuterium at C-1. This result is not necessarily unexpected, since the hydrogen atom at C-2 is now markedly reduced in acidity. Table I summarizes the results of the α addition of lithium reagents to various isocyanides.

Choice of Isocyanide. A convenient synthesis of isocyanides has recently been published.[8] The selection of the isocyanide for the preparation of metallo aldimines is important. Since the α-hydrogen atoms of the isocyanide can readily react with organolithium reagents,[9] it is necessary for the α carbon to be trisubstituted. This may account, in part, for the lack of success by the earlier workers to achieve a simple 1:1 α addition to isocyanides in which the alkyl groups were methyl and ethyl.[3,4] A further limitation on the choice of isocyanide is that the α carbon cannot contain two or more aromatic groups, since the addition of lithium reagents to these isocyanides results in a isocyanide–lithium exchange reaction.[10] Table I lists a number of isocyanides used in this study. In principle any


R = CH_3, Ar

aryl or *tert*-alkyl isocyanide can be used, but the aryl isocyanides tend to oligomerize. The most convenient isocyanide to use is TMBI, owing to its ease of preparation[11] and the fact that it is not offensively malodorous.

Effect of Organometallic Reagent. As can be seen from Table I, primary, secondary, and tertiary aliphatic lithium reagents react very readily with TMBI to produce excellent yields of lithium aldimines or their hydrolysis product, aldehydes. Attempts to improve the yield (45–50%) of the phenyllithium adduct, by varying the reaction temperature and solvent, failed. However, it was noted that by adding a 50% excess of phenyllithium a higher yield of aldimine (70%) was obtained. Vinyllithium and 2-propenyllithium did not give a simple α addition to TMBI. The reaction resulted in a complex mixture of products presumably due to further reaction of the initially formed aldimine.

Based on the results with phenyllithium it appears that the lithium aldimine **1** is in equilibrium with the starting materials, phenyllithium and TMBI. An unfavorable equilibrium is probably also involved in the case of sodium diethylmalonate and lithium phenylacetylide, both of which failed to add to TMBI. If the McEwen–Streitwieser–Applequist–Dessy pK_a scale[12] is related to the results obtained (Table II), one concludes that the conjugate bases of acids with $pK_a < 37$ will not add appreciably to TMBI. This is consistent with the observations by An-

Table II
Relation of Some Entries from the McEwen–Streitwieser–Applequist–Dessy pK_a Scale to the Result When the Organolithium Reagent Is Added to TMBI in a 1:1 Ratio

RLi	pK_a of RH	Results in ether
$(EtOOC)_2CH$	13	No adduct[a]
PhC≡C	18.5	No adduct
Ph	37	50% adduct
Et	42	100% after 45–60 min
n-C_4H_9		100% after 10–20 min
$(CH_3)_2CH$	44	
$EtCH(CH_3)$		100% after 0–5 min
t-C_4H_9	44	100% after 0–5 min

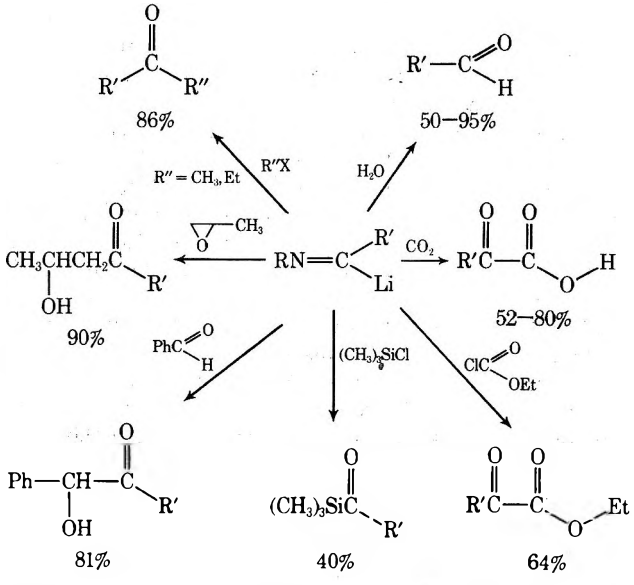
[a] Sodium malonate in THF was treated with TMBI.

selme[13] as well as Meyers[14] and Schöllkopf[15] on the reaction of alkoxide (ROH, p$K_a \cong 18$) with certain isocyanides. In the latter cases[14,15] an equilibrium is established owing to the intramolecular nature of the reaction.

As can be seen from Table III, Grignard reagents do not react as well as lithium reagents. Moreover, phenylmagnesium bromide does not add to any appreciable extent. This observation provides another reason for the lack of success that the earlier workers[3-5] experienced in their attempts to obtain a simple 1:1 α addition to isocyanides. Again, this result may in part be due to an unfavorable equilibrium which, in the case of phenylmagnesium bromide, lies more to the side of the starting reagents.

Reactions of Lithium Aldimines. The lithium aldimine reagents may be viewed as masked acyl carbanions[16] similar in principle to those devised by Corey and Selbach[16] (lithiodiathiane), Stork[17] (magnesium enamines), and Meyers[18] (dihydro-1,3-oxazine system). Thus deuterolysis of 1 provides a simple and inexpensive synthesis of 1-deuterioaldehydes (Table I). Carbonation of 1 yields the corresponding α-keto acid in good yields and treatment of 1 with ethyl chlorocarbonate provides the corresponding ethyl ester.

Chart I
Reactions of Lithium Aldimine[a]



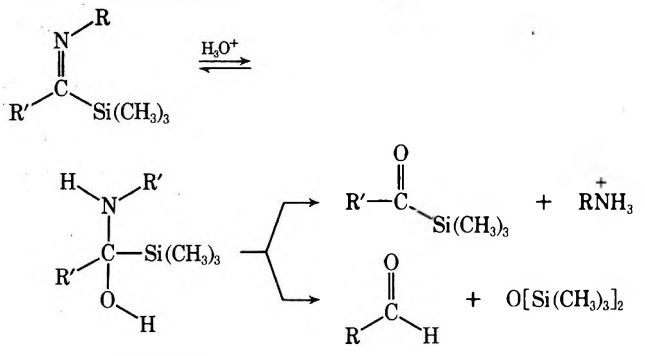
[a] R = 1,1,3,3,-tetramethylbutyl and R′ = n-butyl, ethyl, *sec*-butyl, or phenyl; see Experimental Section.

Chart I shows the different types of reactions that have been carried out using lithium aldimines. Alkylation with ethyl and methyl halides proceeds in good yields to give upon hydrolysis the corresponding ketones. Isopropyl iodide did not alkylate; presumably elimination occurred. However, trimethylsilyl chloride reacted quite well but hydrolysis of the intermediate imine proved difficult. Various attempts (steam distillation from ammonium chloride, sat. hydrochloric acid at 0°, pyruvic acid or dil. hydrochloric acid in methanol at room temperature) resulted in approximately 50% yields of silyl ketone and 50% yield of aldehyde and hexamethylsiloxane. Reaction of 1 with benzaldehyde leads to the formation of α-hydroxy ketones and with propylene oxide to isolable β-hydroxy ketones.

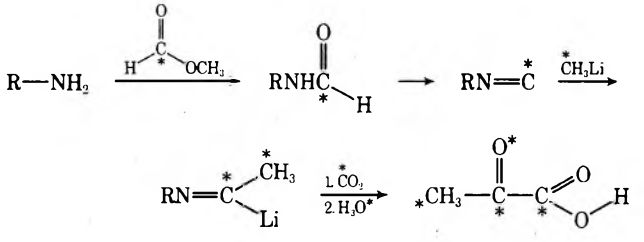
Table III
Aldehydes and α-Keto Acids from Alkyl Grignard Reagents and TMBI

RMgBr[a]	Solvent	Time, hr	% aldehyde (registry no.)	% α-keto acid (registry no.)
sec-Butyl	Ether	3	67 (96)[b]	47 (1460-34-0)
tert-Butyl	THF	24	48	
n-Hexyl	THF	1.5	62 (111-71-7)	26 (328-51-8)
n-Butyl	THF	1.5		34 (2492-75-3)
2-Phenylethyl	THF	1.5	63 (80)[b] (104-53-0)	
Cyclopentyl	THF	1.5	66 (89)[b] (872-53-7)	
Phenyl	THF	18	2	

[a] Concentration of Grignard reagents was *ca.* 0.1 *M*. [b] Per cent deuterium at C-1 as determined by nmr.



It should also be recognized that this system has great potential for the syntheses of labeled compounds. For example, pyruvic acid may be conveniently labeled on four atoms by the following route.



Experimental Section[19]

Bulk solvents were distilled before use. Reagent grade diethyl ether, tetrahydrofuran (THF), and dimethoxyethane were distilled from lithium aluminum hydride prior to use. Infrared spectra were taken neat or in solution (0.5-mm sodium chloride cell) on a Perkin-Elmer Model 247. Nmr spectra were obtained on Varian Associates A-60 and Brucker 90 spectrometers using TMS as internal standard.

Vapor phase chromatography was conducted on an F & M Model 500 programmed temperature gas chromatograph with a thermistor detector. All melting points were taken with a Mel-Temp apparatus. The partial immersion thermometer was calibrated over the range of 81–235°. The addition reactions to *tert*-butyl isocyanide (TBI) and 2,6-dimethylphenyl isocyanide

(DMPI) were carried out in a manner identical with that described for TMBI.

2-(*N*-2-Methylbutylideneamino)-2,4,4-trimethylpentane. A solution of 0.982 g (0.00704 mol) of 1,1,3,3-tetramethylbutyl isocyanide (TMBI) in 70 ml of pentane was treated with 0.00711 mol of *sec*-butyllithium in hexane while stirring at 25°. After 10 min, 0.38 ml of water was added, and the mixture was stirred for 15 min to yield 1.4 g (quantitative yield) of the aldimine after filtering and evaporating off the solvent. The product needed no further purification: bp 85.5° (10 mm); ir (neat) 1667 (m), 1464, 1366, 1223 cm^{-1}; nmr (CCl_4) δ 0.85–1.75 (m, 25), 2.18 (m, 1, CH), 7.50 (d, 1, J = 4.6 Hz, -N=CH).

Anal. Calcd for $C_{13}H_{27}N$: C, 79.11; H, 13.79. Found: C, 79.38; H, 13.68.

2-(*N*-Pentylideneamino)-2,4,4-trimethylpentane. In like manner, 0.5 g (0.00359 mol) of TMBI in pentane was treated with 0.00369 mol of a hexane solution of *n*-butyllithium. A quantitative yield, 0.71 g, of the aldimine was obtained which needed no further purification: bp 89.5° (10 mm); ir (neat) 1667 (m), 1469, 1367, 1223 cm^{-1}; nmr (CCl_4) δ 0.88–1.75 (m, 24), 2.23 (m, 2, CH_2), 7.65 (t, 3, J = 4.5 Hz, -N=CH).

Anal. Calcd for $C_{13}H_{27}N$: C, 79.11; H, 13.79. Found: C, 79.3; H, 13.7.

2-(*N*-*l*-*d*-2-Methylbutylideneamino)-2,4,4-trimethylpentane. The *reaction* was carried out as above. However, D_2O (>99%) was used to quench the lithium aldimine, and 1.4 g of the *l*-*d*-aldimine was obtained: bp 85.5° (10 mm); nmr (CCl_4) δ 0.85–1.75 (m, 25), 2.23 (m, 1), 7.50 (d, <0.02).

***l*-*d*-2-Methylbutanal.** To 35.1 ml (0.2 mol) of TMBI in 300 ml of ether under nitrogen was added, with mechanical stirring at 0° (ice–salt bath), 0.2 mol of *sec*-butyllithium (in hexane) at a rate such that the temperature never exceeded 5°. After an additional 15 min of stirring, 8 ml (0.4 mol) of D_2O (<99%) was injected into the reaction mixture. Filtration of the mixture followed by evaporation of the solvent gave the aldimine, which was distilled, bp 52.5–54° (1.5 mm), to give 36.9 g (0.186 mol). Steam distillation from 200 ml of an oxalic acid solution (2 *M*) gave 16.0 g (0.184 mol) of the *l*-*d*-aldehyde: yield 92% overall; $n^{30}D$ 1.3896; purity 98.6% by vpc analysis (LS-40); isotopic purity 97.9% by nmr analysis; nmr (neat) δ 9.79 (d, 0.021, J = 1.8 Hz); bp 92°; 2,4-DNP mp 128.5–130° (lit.[20] mp 129–130°).

***l*-*d*-2,2-Dimethylpropanal.** Similarly, to 35.1 ml (0.2 mol) of TMBI in 400 ml of ether under nitrogen was added, with mechanical stirring at −15°, 0.2 mol of *tert*-butyllithium (in pentane). D_2O (>99%, 8 ml, 0.4 mol) was injected into the reaction mixtures with continued external cooling. Filtration of the mixture, followed by evaporation of the solvent, gave the aldimine, which was distilled, bp 48–50° (3.2 mm), to give 37.2 g (0.186 mol, 93%). Steam distillation afforded 16.0 g (0.184 mol, 92% yield) of the *l*-*d*-aldehyde: chemical purity 99% by vpc analysis (LS-40); isotopic purity 98% by nmr analysis, nmr (neat) δ 9.33 (s, 0.018); bp 75°; 2,4-DNP mp 211–213° (lit.[20] mp 209–211°).

2-Oxo-3-methylpentanoic Acid. To a stirred solution of 3.76 g (0.027 mol) of TMBI dissolved in 27 ml of ether at 0° under a nitrogen atmosphere was added 0.026 mol of *sec*-butyllithium (in hexane). After 10 min, the solution was added dropwise to an ether slurry of Dry Ice. The solvent was evaporated and the carbonated imine was refluxed in an oxalic acid solution for 15 min. Extraction with methylene chloride, followed by evaporation of solvent, gave 2.8 g (0.021 mol, 80%) of the keto acid: ir (CCl_4) 3410 (m), 1785 (s), 1715 cm^{-1} (s, broad); nmr (CCl_4) δ 11.79 (s, 1); purity 95% by vpc analysis; 2,4-DNP mp 169–170° (lit.[20] mp 171°).

3-Heptanone. To a stirred solution of 20.9 g (0.15 mol) of TMBI dissolved in 150 mol of the THF at −10° under a nitrogen atmosphere was added 0.15 mol of *n*-butyllithium (in hexane). After 30 min the solution was cooled to −75°, and 17 g (0.155 mol) of ethyl bromide in 50 ml of THF was added dropwise. The solution was warmed to 0°, taken up in pentane, washed with water, dried (sodium sulfate), and evaporated to yield an oil which was distilled, bp 68° (0.25 mm). The ketimine, 30.2 g (0.134 mol), was hydrolyzed by steam distillation from an oxalic acid solution (2 *M*) to yield 13.6 g (0.131 mol, 87%): bp 149.5°; ir (neat) 1711 cm^{-1} (s); semicarbazone mp 99.5–101° (lit.[21] mp 99–110°).

1-Hydroxy-1-phenylbutanone. To a stirred solution of 6.95 g (0.05 mol) of TMBI in 50 ml of THF at −10° under a nitrogen atmosphere was added 0.05 mol of ethyllithium (in benzene). After 1 hr, 5.3 g (0.05 mol) of benzaldehyde in 25 ml of THF was added at −50 to −60° (Dry Ice–acetone). The solution was stirred for 1 hr, after which 1.5 ml of water was added. The solvent was filtered and evaporated and the hydroxyl imine was then hydrolyzed with dilute hydrochloric acid and methanol (2 hr) to yield 7.5 g of the crude hydroxy ketone. Distillation gave 6.7 g (0.041 mol, 81%), bp 69° (0.2 mm) [lit.[20] bp 124–128° (11 mm)].

2-Hydroxy-4-octanone. To a stirred solution of 13.9 g (0.1 mol) of TMBI dissolved in 100 ml of THF at −10° under a nitrogen atmosphere was added 0.1 mol of *n*-butyllithium (in hexane). After 30 min 6.85 ml (0.105 mol) of propylene oxide in 25 ml of THF was added dropwise. After continued stirring for 30 min, the solution was taken up in pentane, washed with water, and evaporated to yield the hydroxy ketimine. Hydrolysis to the hydroxy ketone was accomplished by refluxing the imine in a solution of 75 ml of THF, 25 ml of ether, 10 ml of H_2O, 10.5 g (0.2 mol) of ammonium chloride, and 0.1 ml of concentrated hydrochloric acid for 16 hr. Extraction with methylene chloride gave, after drying (sodium sulfate) and evaporating the solvent, 9 g (0.09 mol, 90%) of the hydroxy ketone: bp 61–62° (1 mm) [lit.[22] bp 86–87° (5 mm)]; ir (neat) 3420 (broad), 1703 cm^{-1} (s); nmr (CCl_4) δ 0.7–1.7 (m, 7, $CH_3CH_3CH_2$–), 1.10 (d, 3, J = 6 Hz, CH_3), 2.44 (d, 2, J = 6.3 Hz, CH_2), 2.38 (t, 2, J = 7 Hz, CH_2), 4.03 (s, 1, OH), 4.06 (sextet, 1, J = 6 Hz, CH); *N*-phenylcarbamate mp 55–56°, ir (CCl_4) 3452, 1741, 1718 cm^{-1}.

Anal. (carbamate) Calcd for $C_{15}H_{21}NO$: C, 68.41; H, 8.04; N, 5.32. Found: C, 68.27; H, 8.19; N, 5.24.

2-(*N*-1-Trimethylsilylpropylideneamino)-2,4,4-trimethylpentane. To a stirred solution of 10.5 g (0.075 mol) of TMBI dissolved in 150 ml of THF at −5° under a nitrogen atmosphere was added 0.075 mol of ethyllithium (in benzene). After 45 min the solution was cooled to −75°, and 8.1 g (0.075 mol) of trimethylchlorosilane in 25 ml of THF was added dropwise. The solution was warmed to 0°, and 1.5 ml of saturated sodium carbonate solution was added. The solvent was evaporated to dryness, the residue was triturated with pentane (leaving behind the insoluble salts), and the pentane was evaporated, yielding 17.0 g of the crude imine. Distillation afforded 14.5 g (0.6 mol, 80%) of the product: bp 44.5–45° (0.005 mm); ir (neat) 1601 (m), 1245 (s), 834 cm^{-1} (s); nmr (CCl_4–$CHCl_3$) δ 0.21 [s, 9, $Si(CH_3)_3$], 1.09 [s, 9, $C(CH_3)_3$], 1.14 (t, 3, J = 7.5 Hz, CH_3), 1.39 [s, 6, $C(CH_3)_2$], 1.74 (s, 2, CH_2), 2.50 [q, 2, J = 7.5 Hz, CH_2].

Anal. Calcd for $C_{14}H_{31}NSi$: C, 69.62; H, 12.94; N, 5.80. Found: C, 69.75; H, 12.95; N, 5.81.

Ethyl 2-[*N*-(2-Phenyl-2-butyl)]imino-3-methylpentanoate. To a stirred solution of 4.35 g (27.3 mmol) of 2-phenyl-2-butyl isocyanide dissolved in 50 ml of ether at 0° under nitrogen was added 29.6 ml of 0.97 *M* sec-butyllithium solution in cyclohexane and the mixture was stirred for 30 min. After cooling to −20° the reaction mixture was added dropwise to a stirred solution of 15 g (0.138 mol) of ethyl chlorocarbonate in 80 ml of THF at −78° and then stirred overnight at ambient temperature. Filtration and distillation of the product at reduced pressure gave 5.07 g (64%) of ethyl 2-[*N*-(2-phenyl-2-butyl)]imino-3-methylpentanoate: bp 100–102° (0.25 mm); ir (CCl_4) 1735 (s), 1665 (m, broad), 699 cm^{-1} (m); mass spectrum *m/e* (measured mass) 289.2032 (calcd for $C_{18}H_{27}NO_2$, 289.2041).

Grignard Addition to TMBI. The addition of Grignard reagents was performed in an identical manner with that of the lithium reagents. The results are recorded in Table III. Two typical experiments are given.

3-Methyl-2-oxopentanoic Acid. The Grignard reagent of 2-bromobutane was prepared in the usual manner from 3.62 g (0.150 mol) of magnesium and 20.6 g (0.150 mol) of 2-bromobutane in 150 ml of tetrahydrofuran. To this solution was added 10.4 g (0.75 mol) of TMBI and the mixture was stirred for 4 hr. This solution was transferred under a nitrogen atmosphere to an addition funnel and then added to an ether solution which had been cooled to −78° and saturated with carbon dioxide. After the solution had warmed to room temperature, the mixture was hydrolyzed with dilute hydrochloric acid by refluxing for 15 min. The solution was then extracted with sodium bicarbonate solution, and after acidification of the aqueous layer and extraction with ether, the organic layer was dried over sodium sulfate. Evaporation of the ether gave an oil (7.5 g) which on analysis by nmr gave a yield of 48% 3-methyl-2-oxopentanoic acid and 32% 2-methylbutyric acid. The α-keto acid gave ir (neat) 3410, 2970, 2930, 2870, 1785, 1715, 1510, 1460, 1381, 1340, 1165, 1040, 980, 950 cm^{-1}; nmr (CCl_4) 1.1 (m, 6 H), 1.58 (m, 2 H), 3.28 (m, 1 H), 11.62 (s, 1 H).

***l*-*d*-2-Methylbutyraldehyde.** The Grignard reagent of *sec*-butyl bromide was prepared in the usual manner from 3.62 g (0.150 mol) of magnesium and 20.6 g (0.150 mol) of *sec*-butyl bromide in 150 ml of tetrahydrofuran. To the Grignard solution was added, by means of a syringe, 14.2 g (0.102 mol) of 1,1,3,3-tetramethylbutyl isocyanide and the mixture was stirred at room tempera-

ture for 4 hr. To the solution cooled at 0° was added 6.1 g (0.306 mol) of D_2O followed by an additional 100 ml of water. After extraction with 2 × 100 ml of diethyl ether, the organic layer was washed with a saturated sodium chloride solution and dried over sodium sulfate. After evaporation of the ether the aldimine was distilled, yielding 13.65 g (0.0695 mol, 67.75%), bp 52–54° (1.5 mm).

Steam distillation of the aldimine from 17.2 g (0.14 mol) of aqueous oxalic acid gave 5.85 g (0.069 mol, 67%) yield of *l-d*-2-methylbutyraldehyde. The per cent deuterium incorporation was determined by nmr at δ 9.54 to be 96%.

Acknowledgment. We wish to thank Mr. M. P. Periasamy for his assistance in various aspects of this work.

Registry No.—*sec*-BuBr, 78-76-2; *t*-BuBr, 507-19-7; $CH_3(CH_2)_5Br$, 111-25-1; BuBr, 109-65-9; $PhCH_2CH_2Br$, 103-63-9; cyclopentyl bromide, 137-43-9; *l-d*-2,2-dimethylpropanal, 41162-98-5; 3-heptanone, 106-35-4; 1-hydroxy-1-phenylbutanone, 16183-45-2; 2-hydroxy-4-octanone, 49707-56-4; 2-hydroxy-4-octanone *N*-phenylcarbanilate, 49707-57-5; 2-(*N*-1-trimethylsilylpropylideneamino)-2,4,4-trimethylpentane, 49707-58-6; ethyl 2-[*N*-(2-phenyl-2-butyl)]imino-3-methylpentanoate, 49707-59-7; 2-phenyl-2-butyl isocyanide, 49707-54-2.

References and Notes

(1) This support of this work by a Public Health Service Grant No. 04065 from the National Cancer Institute and, in part, by the National Science Foundation is gratefully acknowledged.
(2) For a preliminary report see H. M. Walborsky, W. H. Morrison, III, and G. E. Niznik, *J. Amer. Chem. Soc.*, **92**, 6675 (1970).
(3) F. Sachs and H. Loevy, *Chem. Ber.*, **37**, 874 (1904).
(4) H. Gilman and L. C. Heckert, *Bull. Soc. Chim. Fr.*, **43**, 224 (1928).
(5) I. Ugi and U. Fetzer, *Chem. Ber.*, **94**, 2239 (1961).
(6) H. M. Walborsky and G. E. Niznik, *J. Amer. Chem. Soc.*, **91**, 7778 (1969).
(7) This result also argues against the formation of a dimetallo aldimine RN=C(Li) CH(Li)R, since this would yield greater than 100% incorporation. However, it should be pointed out that under certain conditions lithium aldimine **1** can undergo a cleavage reaction. See M. P. Periasamy and H. M. Walborsky, *J. Org. Chem.*, **39**, 611 (1974).
(8) H. M. Walborsky and G. E. Niznik, *J. Org. Chem.*, **37**, 187 (1972).
(9) U. Schollkopf and R. Jentsch, *Angew. Chem.*, **85**, 355 (1973), and earlier references cited therein.
(10) H. M. Walborsky, G. E. Niznik, and M. P. Periasamy, *Tetrahedron Lett.*, 4965 (1971).
(11) For a convenient synthesis see G. E. Niznik, W. H. Morrison, III, and H. M. Walborsky, *Org. Syn.*, **51**, 31 (1971).
(12) D. C. Cram, "Fundamentals of Carbanion Chemistry," Academic Press, New York, N. Y., 1965, p 19.
(13) N. Koga, G. Koga, and J. P. Anselme, *Tetrahedron Lett.*, 3309 (1970).
(14) A. I. Meyers and H. W. Adickes, *Tetrahedron Lett.*, 5151 (1969).
(15) F. Gerhart and U. Schöllkopf, *Tetrahedron Lett.*, 6231 (1968).
(16) For interesting reviews see D. Seebach, *Angew. Chem., Int. Ed. Engl.*, **8**, 639 (1969); *Synthesis*, **1**, 17 (1969); E. J. Corey and D. Seebach, *Angew. Chem., Int. Ed. Engl.*, **4**, 1075 (1965).
(17) G. Stork and S. R. Dowd, *J. Amer. Chem. Soc.*, **85**, 2178 (1963); T. Cuvigny and H. Normant, *Bull. Soc. Chim. Fr.*, 3976 (1970).
(18) A. I. Meyers, A. Nabeya, H. W. Adickes, I. R. Politzer, G. R. Malone, A. C. Kovelesky, R. L. Nolen, and R. C. Portney, *J. Org. Chem.*, **38**, 36 (1973), and earlier references cited therein.
(19) Mass spectral analyses were conducted under the supervision of Professor R. C. Dougherty, The Florida State University. Elemental analyses were performed by Beller Laboratories, Gottingen, Germany.
(20) Beilstein, "Handbuch der organische Chemie," Vol. 3, Friedrich Richter, Springer-Verlag, Berlin, 1959.
(21) H. O. House, D. D. Traficante, and R. A. Evans, *J. Org. Chem.*, **28**, 353 (1963).
(22) R. Luft, *Ann. Chim. (Paris)*, **4**, 745 (1959).

Partial Asymmetric Syntheses of Amino Acids Using Lithium Aldimine Precursors[1]

N. Hirowatari and H. M. Walborsky*

Department of Chemistry, Florida State University, Tallahassee, Florida 32306

Received September 10, 1973

Carboxylation or carbethoxylation of the lithium aldimines formed by the α addition of ethyllithium, *sec*-butyllithium, and isopropyllithium to (±)- or (*R*)-(+)-2-phenyl-2-butylisonitrile produced the corresponding α-imino acid or ester. Optically active α-amino acids were synthesized by the reduction, under a variety of conditions, of the α-imino acids and esters.

The use of lithium aldimines as useful synthetic intermediates for the preparation of aldehydes, α-keto acids, ketones, acyloins, α-diketones, and silyl ketones has previously been reported.[2,3] The use of lithium aldimines as precursors for the syntheses of optically active α-amino acids is the subject of this paper.

Results and Discussion

Chart I outlines the procedure used for the preparation of α-amino acids.

The α addition of *sec*-butyllithium, isopropyllithium, and ethyllithium to 2-phenyl-2-butylisonitrile (**1**) proceeds quite readily to yield the corresponding lithium aldimines (**2**). Treatment of **2** with carbon dioxide or ethyl chloroformate produced lithium imino carboxylate salt **3** and ethyl α-imino carboxylate (**5**), respectively. In contrast to the case of imines produced from α-keto acids and α-alkylbenzylamine,[4] attempted concomitant hydrogenation and hydrogenolysis of **3** by the use of palladium hydroxide[5] did not give good results. However, the direct reduction of the corresponding ester **5** did proceed, although in poor yields, to give α-amino acids. Most of the reductions in our studies were carried out in a stepwise fashion using **3** or **3*** as substrate. The double bond was first reduced with either lithium or sodium borohydride, diborane, diisopinocampheylborane, or triisopinocampheylborane and the resulting amine hydrochlorides were debenzylated by catalytic hydrogenolysis to produce the α-amino acids. These results are summarized in Table I.

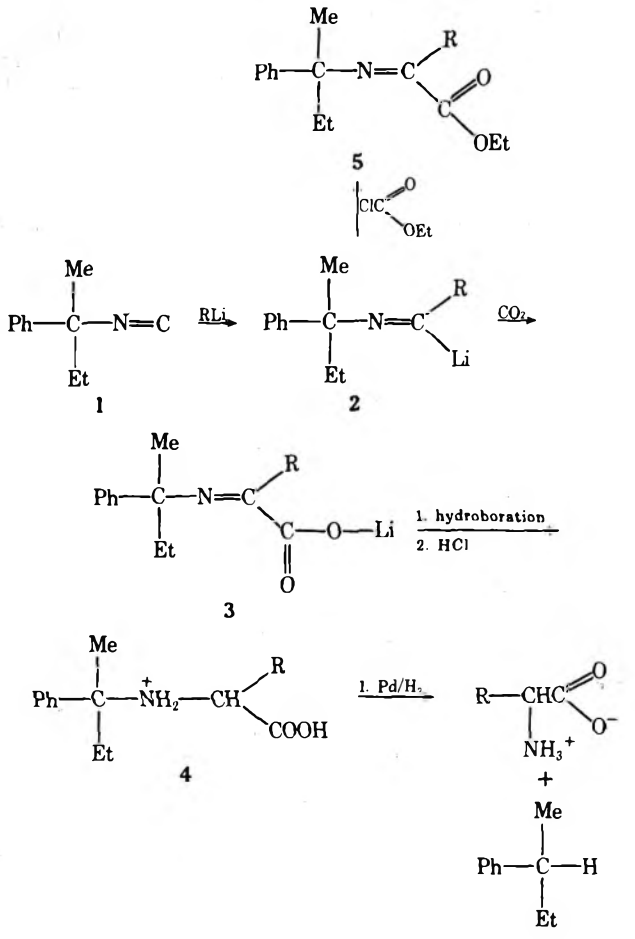
The α-amino acids isolated using standard procedures[6] contained slight impurities[7] which were difficult to remove. Therefore, all optically active α-amino acids were converted into their 2,4-dinitrophenyl derivatives[8] and purified, without attempted resolution, by use of a Celite column.[9] The diastereomeric ratio of racemic isoleucine to alloisoleucine (R = *sec*-butyl) was determined by nmr based upon the α-methine proton absorptions.[10] Catalytic reduction of **5** gave a mixture (ratio 1.3) in which isoleucine predominated, whereas stepwise reduction gave a mixture (ratio 0.7) richer in alloisoleucine. As can also be seen (Table I) the direct hydrogenation and hydrogenolysis of the imino ester **5** or **5*** is not a very satisfactory method, since one obtains a low overall yield and a very small optical induction. The stepwise reduction of **3** or **3*** is the preferred method since the optical yields are reasonably good. It should be recognized that since lithium borohydride and diborane exhibit similar stereoselectivities in the reduction of **3***, the former is obviously the re-

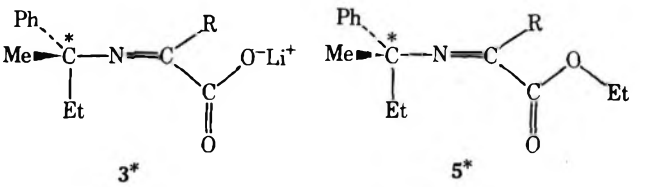
Table I
Amino Acids Obtained by Reduction of Imino Group

Registry no.	Imine reduced	R	Reducing agents[a]	Overall yield, %	Configuration	Free amino acid[b] $[\alpha]^{27}_{546}$	Free amino acid[b] Optical purity, %	DNP amino acid[c] $[\alpha]^{27}D$	DNP amino acid[c] Optical purity, %
49707-59-7	5	*sec*-Butyl	$H_2/Pd(OH)_2$	34	57/43[d]				
49690-14-4	3	*sec*-Butyl	$LiBH_4$	85	42/58[d]				
	3	*sec*-Butyl	B_2H_6	82	42/58[d]				
49690-15-5	3	Ethyl	$LiBH_4$	70					
	3	Ethyl	B_2H_6	64					
	3	Ethyl	(−)-R_2BH[e]	57	*S*[h]	+2.9	11 (12)	+15.0	16 (17)
	3	Ethyl	(+)-R_2BH[f]	58	*R*[i]	−3.5	13 (15)	−13.3	14 (16)
	3	Ethyl	(−)-$R_2BH \cdot RBH_2$[e]	45	*S*	+2.0	8 (9)	+8.1	9 (10)
49844-62-4	5*	Ethyl	$H_2/Pd(OH)_2$	23	*R*	−0.8	3	−8.4	9
49844-63-5	3*	Ethyl	$LiBH_4$[g]	77	*R*	−13.7	52	−52.1	55
	3*	Ethyl	$LiBH_4$	63	*R*	−15.0	57	−59.3	63
	3*	Ethyl	B_2H_6[g]	66	*R*	−14.5	55	−52.6	56
	3*	Ethyl	B_2H_6	57	*R*	−14.6	55	−58.3	62
49690-16-6	3	Isopropyl	$NaBH_4$	83					
	3	Isopropyl	(−)-R_2BH[e]	42	*S*[j]	+12.6	40 (43)	+41.7	42 (45)
	3	Isopropyl	(+)-R_2BH[f]	43	*R*[k]	−10.4	33 (37)	−35.2	35 (39)
	3	Isopropyl	(−)-$R_2BH \cdot RBH_2$[e]	38	*S*	+8.7	28 (30)	+34.7	35 (37)
49844-64-6	5*	Isopropyl	$H_2/Pd(OH)_2$	29	*R*	−0.2	0.6	−3.6	4
49844-65-7	3*	Isopropyl	$LiBH_4$	80	*R*	−17.6	56	−62.3	62
	3*	Isopropyl	B_2H_6	81	*R*	−16.6	53	−54.5	54

[a] All metal hydride reductions were followed by $Pd(OH)_2$ hydrogenolysis. [b] Specific rotations of all free amino acids were obtained using 5 *N* HCl as solvent; optical purities were calculated using for R = *sec*-butyl, $[\alpha]^{27}_{546}$ +26.4° (*c* 1.47, 5 *N* HCl); R = isopropyl, $[\alpha]^{27}_{546}$ +31.2° (*c* 1.57, 5 *N* HCl); values in parentheses are corrected for the optical purity of α-pinene, 93.5% [(+)-α-pinene, 89%]. [c] Based on the observed specific rotation of authentic samples: DNP-(*S*)-butyrine, $[\alpha]^{27}D$ +94.1° (*c* 0.27, 1 *N* NaOH); DNP-(*S*)-valine, $[\alpha]^{21}D$ +100.2° (*c* 0.26, 1 *N* NaOH). Values in parentheses are corrected for the optical purity of α-pinene. [d] The diastereomeric ratio of isoleucine to alloisoleucine is based upon the α-methine nmr proton absorption. [e] Prepared from (−)-α-pinene and diborane. [f] Prepared from (+)-α-pinene and diborane. [g] Worked up under alkaline conditions. [h] Registry no.: free amino acid, 1492-24-6; DNP amino acid, 4470-69-3. [i] Registry no.: free amino acid, 2623-91-8; DNP amino acid, 72-18-4. [j] Registry no.: free amino acid, 6367-34-6; DNP amino acid, 1694-97-9. [k] Registry no.: free amino acid, 640-68-6; DNP amino acid, 37696-35-8.

Chart I
Asymmetric Syntheses of α-Amino Acids





agent of choice. Moreover, based on optical yields, the reduction of 3* with achiral borohydrides is superior to the reduction of 3 with chiral borohydrides. It should also be noted that reduction of (*R*)-3* and (*R*)-5* leads to the formation of *R* amino acids.

The results of the reduction of 3 with chiral borohydrides lead to the following observations. (1) Diisopinocampheylborane and triisopinocampheylborane prepared from (−)-α-pinene lead to the formation of *S* amino acids. (2) Diisopinocampheylborane exhibits slightly higher optical yields than triisopinocampheylborane.[11] (3) Higher optical yields are observed for valine (R = isopropyl) than for butyrine (R = ethyl), presumably owing to the greater steric interaction of the isopropyl group.

Interpretation of our results in terms of transition state models postulated[12] for asymmetric reduction of olefins is not possible, since our system is more complicated. The addition may not involve a four-centered transition state[12] owing to the possible complexing of the borane with the nonbonding pair of electrons on the nitrogen. Moreover, it is also difficult to assess at this time the effect of geometric isomerism of these imines on the steric course of the reduction.

Experimental Section

Melting points were determined in capillary tubes using a Mel-Temp apparatus with a calibrated thermometer. Infrared spectra were obtained with a Perkin-Elmer Model 257 infrared spectrophotometer. Solution spectra were run using either carbon tetrachloride or chloroform solutions in a 0.5-mm sodium chloride cell.

Optical rotations were measured at the 546-nm line of mercury and D line of sodium on a O. C. Rudolph and Sons Inc. Model 80 No. 714 polarimeter. Nmr spectra were obtained on a Varian Associates A-60 and a Brucker 90 spectrometer. Nmr spectra of amino acids were determined as a solution in deuterium oxide with TMS as external standard using a Brucker 90 spectrometer.

2-Amino-3-methylpentanoic Acid (Isoleucine and Alloisoleucine). A. Lithium Borohydride Reduction. To a stirred solution of 1.59 g (10 mmol) of racemic 2-phenyl-2-butyl isonitrile dissolved in 500 ml of anhydrous ether at 0° under a nitrogen atmosphere was added rapidly 11.0 ml of 0.97 *M* *sec*-butyllithium solution in cyclohexane. The mixture was stirred at 0° for 30 min and added dropwise to an excess of carbon dioxide in ether at −20°. The solvent was removed *in vacuo* to give the carboxylated imine [ir ($CHCl_3$) 1620 cm^{-1} (s)], which was dissolved in 50 ml of anhydrous tetrahydrofuran (THF), treated with 0.22 g (10 mmol) of lithium borohydride at −10°, and stirred at room temperature for 2 days. After the mixture was cooled to −15°, dilute hydrochloric acid was added to decompose excess lithium borohydride. The solvent was removed *in vacuo* and the remaining aqueous solution was extracted with ether and concentrated to dryness. Three 20-ml portions of water were added and evaporated to remove hydrochloric acid, and three 20-ml portions of absolute ethanol and then four 30-ml portions of benzene were added and evaporated to remove water. The residue was extracted thoroughly with anhydrous benzene to filter off the boron compound. Removal of the solvent afforded crude 2-[*N*-(2-phenyl-2-butyl)]amino-3-methylpentanoic acid hydrochloride in quantitative yield as a white powder: mp 57–119°; ir ($CHCl_3$) 3400–2400 (broad), 1710 (m), and 1570 cm^{-1} (s). An analytical sample was obtained by recrystallization from ether–ethyl acetate: mp 95–129°; ir (KBr) 3400–2360 (broad), 1730 (m), 1565 (s), 765 (s), and 700 cm^{-1} (s).

Anal. Calcd for $C_{16}H_{26}ClNO_2$: C, 64.09; H, 8.74; N, 4.67. Found: C, 64.26; H, 8.85; N, 4.54.

The crude hydrochloride (1.44 g, 4.81 mmol) dissolved in 50 ml of 95% ethanol was subjected to hydrogenolysis using 0.5 g of palladium hydroxide on carbon catalyst[5] and 2 ml of 0.01 *N* hydrochloric acid. The mixture was stirred under 3.5 atm pressure of hydrogen at room temperature for 12 hr. The catalyst was filtered and washed with 95% ethanol and the combined filtrates were evaporated *in vacuo*. The residue, dissolved in 50 ml of water, was extracted with ether and the aqueous layer was concentrated to 10 ml. The amino acids were isolated according to a published procedure[6] and there was obtained 0.54 g (85% overall yield based on the isonitrile) of the product, identified by comparison of the ir spectrum in potassium bromide and the nmr spectrum in deuterium oxide with those of an authentic sample. The diastereomeric ratio of isoleucine to alloisoleucine was 42:58 based upon the α-methine proton nmr absorptions.

B. Hydroboration. The carbonated imine (10 mmol), prepared as described above, was dissolved in 40 ml of THF and treated with 7.4 ml of a 1.44 *M* solution of diborane in THF at −15° and the mixture was stirred at 2–3° for 3 hr.[13] After cooling to −20° dilute hydrochloric acid was added and the mixture was worked up as described above to afford the hydrochloride in quantitative yield: mp 55–125°; ir ($CHCl_3$) was superimposable with that of the hydrochloride of an authentic sample.

The crude hydrochloride (1.46 g, 4.87 mmol) was hydrogenolyzed according to the procedure described above and 0.52 g (82% overall yield) of the amino acids was obtained. The diastereomeric ratio was 42:58.

C. *Via* **Ester.** To a stirred solution of 4.35 g (27.3 mmol) of the racemic isonitrile dissolved in 50 ml of ether at 0° under a nitrogen atmosphere was added rapidly 29.6 ml of 0.97 *M* *sec*-butyllithium solution in cyclohexane and the mixture was stirred for 30 min at 0°. After cooling to −20° the mixture was added dropwise to a stirred solution of 15.0 g (0.138 mol) of ethyl chloroformate in 80 ml of THF at −78° and stirred overnight at room temperature. Filtration of lithium chloride and distillation of the residue under reduced pressure gave 5.07 g (64.1%) of ethyl 2-[*N*-(2-phenyl-2-butyl)]imino-3-methylpentanoate: bp 100–102° (0.25 mm); ir (CCl_4) 1735 (s), 1665 (m, broad), 699 cm^{-1} (m); mass spectrum *m/e* (measured mass) 289.2032 (calcd for $C_{18}H_{27}NO_2$, 289.2041).

A mixture of 2.02 g (7 mmol) of the imino ester and 1.0 g of palladium hydroxide on carbon catalyst in 30 ml of anhydrous benzene was shaken under 3.5 atm pressure of hydrogen at room temperature for 3 days. The catalyst was filtered and washed with benzene. The combined filtrates were extracted with 50 ml of 3 *N* hydrochloric acid. From the organic layer there was obtained 0.97 g of a mixture which consisted of 35% of *sec*-butylbenzene and 23% of ethyl 3-methyl-2-oxopentanoate. The latter was obtained by hydrolysis of the imine ester with dilute hydrochloric acid in 66.2% yield: bp 66–67° (15 mm) [lit.[14] bp 78–79° (15 mm)]; ir (CCl_4) 1735 cm^{-1} (s, broad); nmr (CCl_4) 0.90 (t, 3, J = 7 Hz), 1.09 (d, 3, J = 7 Hz), 1.35 (t, 3, J = 7 Hz), 1.63 (m, 2), 3.03 (sextet, 1), 4.26 (q, 2, J = 7 Hz); 2,4-DNP mp 106–106.5° (needles from ethanol); ir (CCl_4) 3290 (w), 3210 (w, broad), 3100 (w), 1735 (w), 1710 (m), 1625 (s), 1510 (s), 1345 cm^{-1} (s).

Anal. (2,4-DNP) Calcd for $C_{14}H_{18}N_4O_6$: C, 49.70; H, 5.36; N, 16.56. Found: C, 49.60; H, 5.34; N, 16.55.

The aqueous layer was refluxed for 6 hr, extracted with ether, and concentrated to dryness. To the residue 30 ml of water was added and evaporated and the residue was dissolved in 10 ml of water and desalted to afford 0.48 g (52%, 34% overall yield based on the isonitrile) of the amino acid. The diastereomeric ratio was 57:43.

2-Aminobutyric Acid (Butyrine). A. Hydroboration. To a stirred solution of 0.80 g (5 mmol) of 2-phenyl-2-butyl isonitrile dissolved in 30 ml of anhydrous ether at 0° under a nitrogen atmosphere was added rapidly 5.1 ml of 1.0 *M* ethyllithium solution in benzene and the mixture was stirred at 0° for 1 hr. After cooling to −78° the mixture was added to a large excess of carbon dioxide in ether at −40°. The solvent was evaporated to leave the carbonated imine [ir ($CHCl_3$) 1630 cm^{-1} (s)], which was dissolved in 50 ml of THF and treated with 4.0 ml of 1.3 *M* diborane solution in THF at −15°. The mixture was stirred at 2–3° for 3 hr and decomposed with dilute hydrochloric acid. After removal of THF, the aqueous solution was extracted with ether, concentrated to dryness, and worked up as previously described to yield 1.17 g (86.2%) of crude 2-[*N*-(2-phenyl-2-butyl)]aminobutyric acid hydrochloride as a white powder: mp 66–113°; ir ($CHCl_3$) 3400–2400 (broad), 1715 (m), and 1575 cm^{-1} (s). An analytical sample was obtained by recrystallization from ether–ethyl acetate–acetone: mp 173–175°; ir (KBr) 3530 (w, broad), 2450 (w, broad), 3090 (m, broad), 2740 (s, broad), 2510 (m), 2420 (m), 1720 (m), and 1570 cm^{-1} (s).

Anal. Calcd for $C_{14}H_{22}ClNO_2$: C, 61.87; H, 8.16; N, 5.15. Found: C, 61.63; H, 8.14; N, 5.14.

The crude hydrochloride (1.14 g, 4.2 mmol) was subjected to hydrogenolysis to give 0.32 g (64% overall yield) of the amino acid. Identity was confirmed by comparison of the infrared spectrum and nmr spectrum with those of an authentic sample.

B. Lithium Borohydride Reduction. The carbonated imine (10 mmol) prepared as described above was dissolved in 50 ml of THF and treated with 0.22 g (10 mmol) of lithium borohydride at −10°. The mixture was stirred at room temperature for 2 days. The work-up, as previously described, furnished 2.27 g (83.6%) of the crude hydrochloride: mp 85–119°; superimposable ir spectrum with that of an authentic sample.

The crude hydrochloride (1.16 g, 4.27 mmol) was hydrogenolyzed in the usual way to yield 0.37 g (70% overall yield) of the amino acid.

2-Amino-3-methylbutyric Acid (Valine). To a stirred solution of 1.11 g (7 mmol) of 2-phenyl-2-butyl isonitrile dissolved in 50 ml of ether at 0°, under a nitrogen atmosphere, was added rapidly 6.4 ml of a 1.2 *M* isopropyllithium solution in pentane. The mixture was stirred at 0° for 30 min and added dropwise to an excess of carbon dioxide in ether at −30°. The solvent was removed *in vacuo* to give the carbonated imine [ir ($CHCl_3$) 1635 cm^{-1} (s, broad)], which was dissolved in 50 ml of anhydrous methanol; 0.3 g (8 mmol) of sodium borohydride was added and the mixture was stirred at room temperature for 3 days. After removal of the solvent *in vacuo* the residue was dissolved in water and extracted with ether. The aqueous layer was made acidic with dilute hydrochloric acid, extracted with ether, concentrated to dryness, and worked up as previously described to yield 1.94 g (97%) of crude hydrochloride as a white powder: mp 103–143°; ir ($CHCl_3$) 3400–2400 (broad), 1710 (s), and 1565 cm^{-1} (s).

The 1.61 g (5.63 mmol) of the crude hydrochloride afforded 0.57 g (83% overall yield) of the amino acid. Identity was confirmed by comparison of the infrared spectrum in potassium bromide with that of an authentic sample.

Asymmetric Syntheses of Amino Acids Using Optically Active Hydroborating Agents. Diisopinocampheylborane[15] and triisopinocampheyldiborane[12] were prepared according to the published procedure utilizing (−)-α-pinene ($[\alpha]^{20}D$ −48.2°, 93.5% optical purity) and (+)-α-pinene ($[\alpha]^{20}D$ +46°, 89% optical purity).

2-Amino-3-methylbutyric Acid (Valine). A. (+)-Diisopinocampheylborane Reduction. To a solution of 3.3 g (24.3 mmol) of (−)-α-pinene in 20 ml of THF was added 11.5 ml of a 0.91 *M* solution of diborane (5.2 mmol of B_2H_6) in THF at 0° and the reaction mixture was stirred for 4 hr at 0°.

The carbonated imine was prepared in the usual way using 0.80 g (5 mmol) of the racemic isonitrile, 4.2 ml of 1.25 *M* isopropyllithium solution in pentane, and then carbon dioxide. To the optically active hydroborating agent in THF was added, at −10°, the solution of the carbonated imine in 30 ml of THF and the reaction mixture was stirred for 3 weeks at room temperature. After the mixture was cooled to −10°, 50 ml of dilute hydrochloric acid was added and the THF was removed under reduced pressure. Ether was added to the remaining aqueous solution and the solution was stirred overnight at room temperature. The aqueous layer was separated, concentrated to dryness, and worked up as previously described to afford 1.20 g of the crude hydrochloride, mp 78–123°.

The hydrochloride (1.17 g, 4.1 mmol) was hydrogenolyzed in the usual way to give 0.24 g (42% overall yield) of valine, identified by the infrared spectrum in potassium bromide:[16] $[\alpha]^{27}_{546}$ +12.6° (*c* 3.1, 5 *N* HCl), optical purity 40%; DNP-valine: $[\alpha]^{27}_{D}$ +41.7° (*c* 0.27, 1 *N* NaOH), optical purity 42%.

B. (−)-Diisopinocampheylborane Reduction. The reaction was carried out in the same way as described above using (+)-α-pinene instead of (−) enantiomer. Overall yield of the amino acid was 43%: $[\alpha]^{27}_{546}$ −10.4° (*c* 3.1, 5 *N* HCl); optical purity 35%.

C. Triisopinocampheyldiborane Reduction. To 12.1 ml of a 0.64 *M* solution of diborane (7.7 mmol of B_2H_6) in THF was added a solution of 3.1 g (23 mmol) of (−)-α-pinene in 10 ml of THF at 0° and the reaction mixture was stirred for 3 hr at 0°. To this mixture was added a solution of 7 mmol of the carbonated imine, and the reaction mixture was stirred at 0° for 3 days. The previously described work-up gave 1.83 g of the hydrochloride, which was subjected to hydrogenolysis to yield 0.31 g (38% overall yield) of valine: $[\alpha]^{27}_{546}$ +8.7° (*c* 3.0, 5 *N* HCl), optical purity 28%; DNP-valine $[\alpha]^{27}_{D}$ +34.7° (*c* 0.27, 1 *N* NaOH), optical purity, 35%.

2-Aminobutyric Acid (Butyrine). A. (+)-Diisopinocampheylborane Reduction. To a solution of 4.0 g (29.4 mmol) of (−)-α-pinene in 20 ml of THF was added 9.9 ml of a 1.27 *M* solution of diborane (6.3 mmol of B_2H_6) in THF at 0° and the reaction mixture was stirred for 4 hr at 9°.

To the optically active hydroborating agent in THF was added the solution of the carbonated imine (6 mmol) in 30 ml of THF at −10° and the reaction mixture was stirred for 2 weeks at room temperature. After the mixture was cooled to −10°, 50 ml of dilute hydrochloric acid was added. The THF was removed under reduced pressure, and the remaining aqueous layer was worked up as previously described to afford 1.33 g of the crude hydrochloride, mp 82–142°.

The hydrochloride (1.32 g, 4.86 mmol) was hydrogenolyzed in the usual way to give 0.35 g (57% overall yield) of butyrine, identified by the infrared spectrum in potassium bromide: $[\alpha]^{27}_{546}$ +2.9° (*c* 3.0, 5 *N* HCl), optical purity 11%; DNP-butyrine $[\alpha]^{27}_{D}$ +15.0° (*c* 0.28, 1 *N* NaOH), optical purity 16%.

B. (−)-Diisopinocampheylborane Reduction. The reaction was carried out in the same way as described above using (+)-α-pinene instead of (−)-α-pinene. Overall yield of the amino acid was 58%: $[\alpha]^{27}_{546}$ −3.5° (*c* 3.2, 5 *N* HCl), optical purity 13%; DNP-butyrine $[\alpha]^{27}_{D}$ −13.3 (*c* 0.25, 1 *N* NaOH), optical purity 14%.

Asymmetric Syntheses of Amino Acids Using Optically Active (*R*)-(+)-2-Phenyl-2-butyl Isonitrile. Optically pure (*R*)-(+)-2-phenyl-2-butyl isonitrile, $[\alpha]^{24}_{546}$ +2.87° (*c* 3, dioxane), was prepared according to the published procedure.[17]

The reduction procedures described previously were repeated on the optically active (*R*)-(+)-isonitrile and the identity of amino acids was confirmed by comparison of the infrared spectrum with that of an authentic sample.[16] The results are summarized in Table I.

Registry No.—(±)-**1**, 49690-21-3; (*R*)-**1**, 32528-86-2; isoleucine, 443-79-8; alloisoleucine, 3107-04-8; 2-[*N*-(2-phenyl-2-butyl)]amino-3-methylpentanoic acid hydrochloride, 49690-23-5; ethyl 3-methyl-2-oxopentanoate, 26516-27-8; ethyl 3-methyl-2-oxopentanoate 2,4-dinitrophenylhydrazone, 49690-24-6; 2-[*N*-(2-phenyl-2-butyl)]aminobutyric acid hydrochloride, 49690-25-7; butyrine, 80-60-4; valine, 516-06-3; 2-[*N*-(2-phenyl-2-butyl)]amino-3-methylbutyric acid hydrochloride, 49690-26-8; (*S*)-2-[*N*-[(*R*)-2-phenyl-2-butyl]]amino-3-methylbutyric acid hydrochloride, 49690-27-9; (*S*)-2-[*N*-[(*R*)-2-phenyl-2-butyl]]aminobutyric acid hydrochloride, 49690-28-0.

References and Notes

(1) The support of this work by Public Health Service Grant No. 04065 from the National Cancer Institute is gratefully acknowledged.
(2) H. M. Walborsky and G. E. Niznik, *J. Amer. Chem. Soc.*, **91**, 7778 (1969).
(3) H. M. Walborsky, W. H. Morrison, III, and G. E. Niznik, *J. Amer. Chem. Soc.*, **92**, 6675 (1970); G. E. Niznik, W. H. Morrison, III, and H. M. Walborsky, **39**, 600 (1974).
(4) J. D. Morrison and H. S. Mosher, "Asymmetric Organic Reactions," Prentice-Hall, Englewood Cliffs, N. J., 1971, p 305.
(5) R. G. Hiskey and R. C. Northrop, *J. Amer. Chem. Soc.*, **83**, 4798 (1961).
(6) (a) E. J. Corey, R. J. McCaully, and H. S. Sachdev, *J. Amer. Chem. Soc.*, **92**, 2476 (1970); (b) E. J. Corey, H. S. Sachdev, J. Z. Gougoutas, and W. Saenger, *ibid.*, **92**, 2488 (1970).
(7) (a) K. Harada, *J. Org. Chem.*, **32**, 1790 (1967); (b) K. Harada and T. Yoshida, *Bull. Chem. Soc. Jap.*, **43**, 921 (1970).
(8) K. R. Rao and H. A. Sober, *J. Amer. Chem. Soc.*, **76**, 1328 (1954).
(9) (a) J. C. Perrone, *Nature (London)*, **167**, 513 (1951); (b) A. Courts, *Biochem. J.*, **58**, 70 (1954); (c) ref 7b and references cited therein.
(10) In the nmr spectra authentic L-isoleucine gave the α-methine proton absorption at 4.10 ppm as a doublet with a coupling constant of 3.7 Hz, whereas the authentic mixture of racemic isoleucine and alloisoleucine exhibited two doublets at 4.11 (J = 3.7 Hz) and 4.18 ppm (J = 3.6 Hz).
(11) In the asymmetric hydroboration of Δ^1-piperidines with both reagents, no difference in the optical activities was observed: D. R. Boyd, M. R. Grundon, and W. R. Jackson, *Tetrahedron Lett.*, 2101 (1967).
(12) H. C. Brown, N. R. Ayyangar, and G. Zweifel, *J. Amer. Chem. Soc.*, **86**, 1071 (1964); D. R. Brown, S. F. A. Kettle, J. McKenna, and J. M. McKenna, *Chem. Commun.*, 667 (1967); A. Streitwieser, Jr., L. Verbit, and R. Bittman, *J. Org. Chem.*, **32**, 1530 (1967).
(13) G. Zweifel, N. R. Ayyangar, T. Munekata, and H. C. Brown, *J. Amer. Chem. Soc.*, **86**, 1076 (1964).
(14) R. Locquin, *Bull. Soc. Chim. Fr.*, **35**, 964 (1966).
(15) H. C. Brown, M. R. Ayyangar, and G. Zweifel, *J. Amer. Chem. Soc.*, **86**, 397 (1964).
(16) The authentic sample was prepared by dissolving 55 mg of (*R*)-valine and 45 mg of (*RS*)-valine in water and evaporating the solution to dryness. An authentic sample of butyrine was prepared in a similar manner.
(17) H. M. Walborsky and G. E. Niznik, *J. Org. Chem.*, **37**, 187 (1972).

Cyclopropanes. XXXIV. Ring Enlargements and Rearrangements from Carbanionic α Additions to Isocyanides[1]

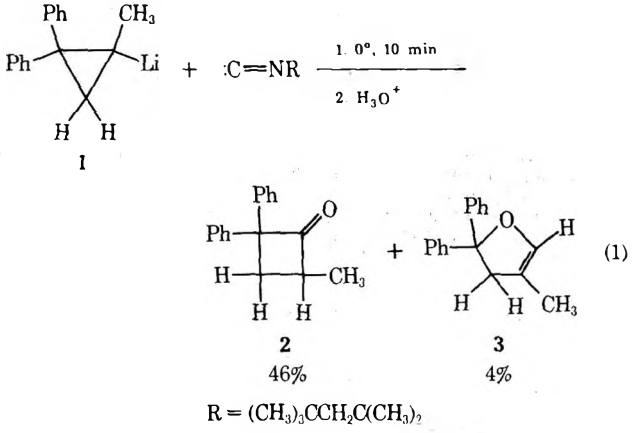
G. E. Niznik and H. M. Walborsky*

Department of Chemistry, Florida State University, Tallahassee, Florida 32306

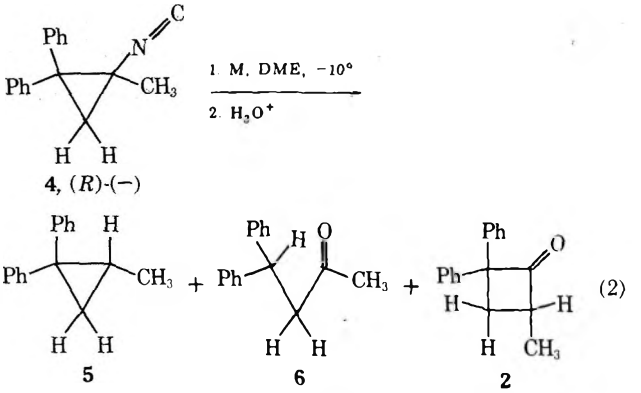
Received September 10, 1973

The reaction of 1-methyl-2,2-diphenylcyclopropyllithium (1) with 1,1,3,3-tetramethylbutyl isocyanide resulted in a ring enlargement to yield 2,2-diphenyl-4-methylcyclobutanone (2). A similar ring enlargement was observed when 1-methyl-2,2-diphenylcyclopropyl isocyanide (4) was treated with lithium or sodium metal in dimethoxyethane. In this latter reaction one also obtained an equal amount of rearranged 4,4-diphenyl-2-butanone (6). Reaction of 4 with a solution of sodium in liquid ammonia produced 1,1-diphenylbutane (10) and 2-methyl-4,4-diphenylpyrolidine (11). Reaction pathways leading to the formation of the ring-expanded and rearranged products are discussed.

We have previously shown that the addition of lithium alkyls to isocyanides leads to the formation of lithium aldimines.[2] The lithium aldimine intermediate can be used for the preparation of *l*-*d*-aldehydes, ketones, α-keto acids and esters, and α- and β-hydroxy ketones.[3] However, we found that 2,2-diphenyl-1-methylcyclopropyllithium (1) did not undergo a simple α addition to 1,1,3,3-tetramethylbutyl isocyanide (TMBI) to give the expected aldimine; rather an enlargement of the cyclopropyl ring occurred to give the unexpected cyclobutanone 2 and the dihydrofuran 3 after hydrolysis (eq 1).



(1)



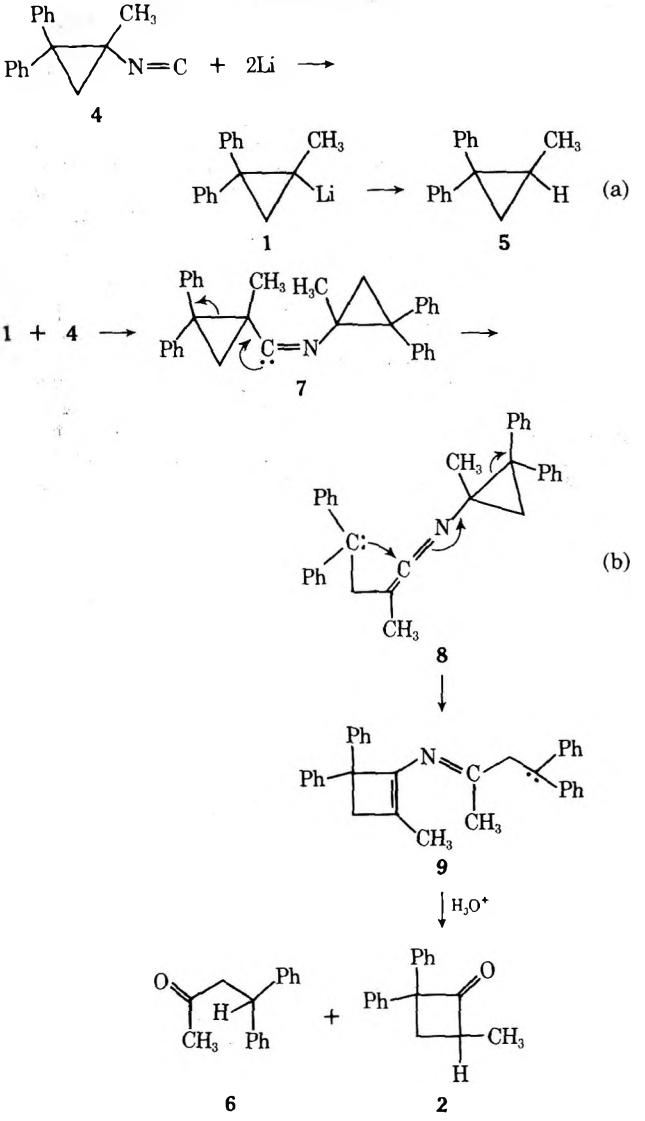
(2)

M	% 5 (optical purity)	% 6	% 2
Li	11 (12%)	44	42
Na	13 (64%)	42	40

This result and the work with lithium aldimines was concurrent with a general study of the dissolving metal reductions of isocyanides.[4] (*R*)-(−)-2,2-Diphenyl-1-methylcyclopropyl isocyanide (4) was prepared to investigate its reduction in a manner similar to that performed on the corresponding cyclopropyl halides.[5] The isocyanide group was being viewed as a pseudo-halogen.

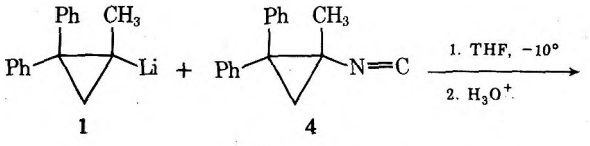
It was found that when 4 was treated with a lithium or sodium dispersion in dimethoxyethane (DME), 1-methyl-2,2-diphenylcyclopropane (5) was obtained with overall retention of configuration (eq 2). However, the major products of the reaction were 4,4-diphenyl-2-butanone (6) and 2,2-diphenyl-4-methylcyclobutanone (2). Presumably 6 could have arisen from ring opening[5b] followed by reductive cleavage of the isocyanide group, but 2 was definitely the result of an unusual rearrangement. A clue was provided by the observation that both 6 and 2 appeared in roughly equal quantities in the product mixture. This sug-

Chart I
Formation of 2,2-Diphenyl-4-methylcyclobutanone and 4,4-Diphenyl-2-butanone

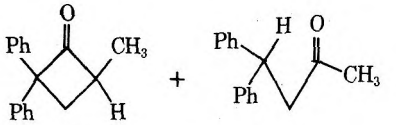


gested that they both may have originated from a common intermediate. The hypothesis, which was adopted, is illustrated in Chart I.

The intermediate **9** is a logical precursor of **2** and **6** and the anionic addition to the ketenimine **8** to form **9** is reasonable. Protonated **9** could not be isolated and purified; however, the spectral data of the crude mixture (see Experimental Section) showed the presence of a compound of mass 441 whose nmr spectrum contained the characteristic benzhydryl triplet at δ 4.44 and the adjacent methylene doublet at δ 2.94, imitating the pattern found in the nmr spectrum of **6**. To test the validity of the hypothesis that **1** added to **4** *via* an α addition, the cyclopropyllithium compound was prepared from 1-bromo-1-methyl-2,2-diphenylcyclopropane in ether. This solution was added to the cyclopropyl isocyanide **4** to give, after hydrolysis, the two ketones **2** and **6** (eq 3).

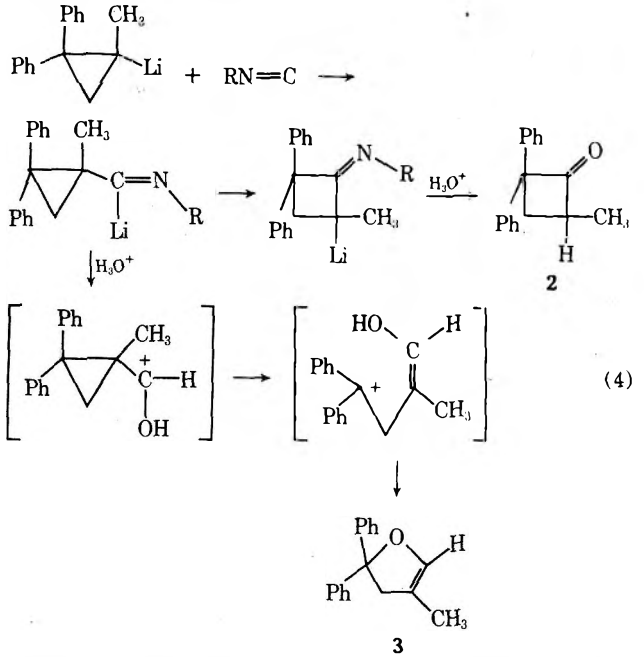


1 4



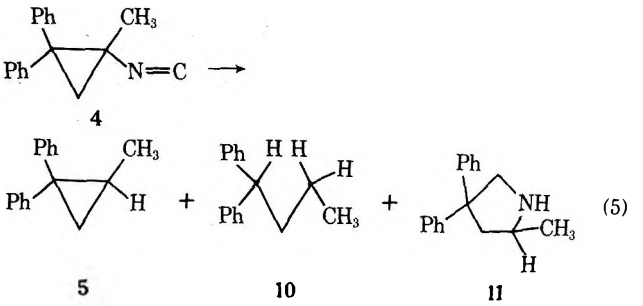
2 6
17% 15% (3)

The results represented in eq 1 can be rationalized in the following way (eq 4).



The cyclopropyllithium **1** adds to form the lithium aldimine intermediate, which undergoes ring enlargement to form the lithiocyclobutanone imine. The formation of **3** probably results from hydrolysis of a small amount of the lithium aldimines as shown. This pathway to **3** was verified by treating 2,2-diphenyl-1-methylcyclopropanecarboxaldehyde with acid to give **3**. The results illustrated in eq 1 together with 3 indicate that **1** is the origin of **2** and that **4** is the precursor to **6**.

Another novel ring expansion was observed when the cyclopropyl isocyanide **4** was reduced with sodium in liquid ammonia (eq 5). Again the principal product was not the expected cyclopropane **5**. Instead, 1,1-diphenylbutane (**10**) and 3,3-diphenyl-5-methylpyrrolidine (**11**) were obtained as the major products. One can rule out the fact that **10** may have arisen as a result of Birch reduction of the cyclopropane **5**, for it had already been shown that under the conditions used in this experiment (8–10% Na) no ring-opened products are produced.[5b]

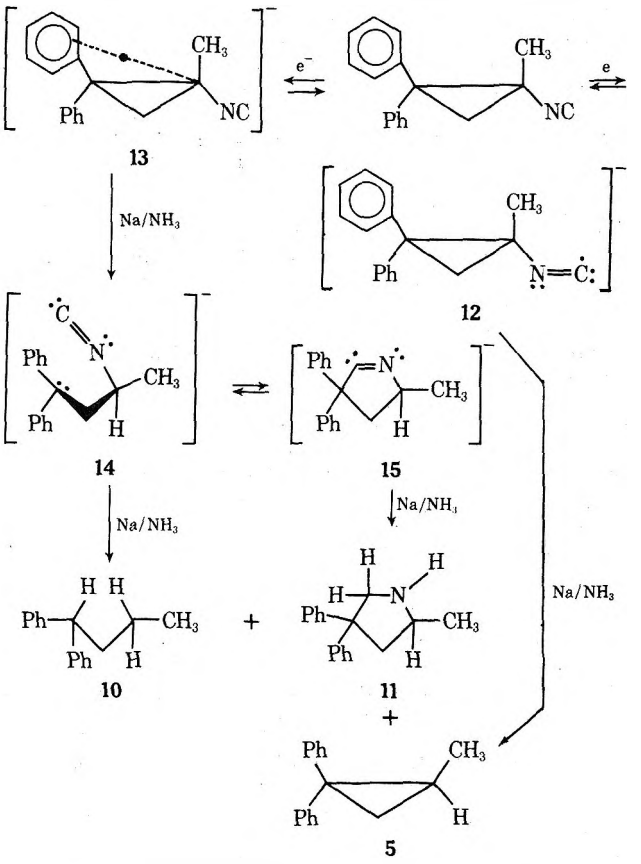


5 10 11

Form	% Na	% 5	% 10	% 11
Powder	8	4	41	55
Dissolved	10	0	13	87

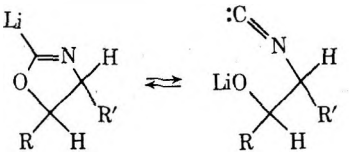
To explain the product mixture it is proposed (Chart II) that two radical anions are produced as primary intermediates, **12** and **13**. In ether solvents an electron transfer occurs at the isocyanide site to give the expected radical anion, **12**. Further reduction gives the expected cyclopropane **5**. However, in the liquid ammonia system, we feel that solvation at the isocyanide site raises the potential of the system so that the preferred site for the electron transfer is at one of the aromatic phenyl groups to produce the radical anion **13**. A similar occurrence was also observed during the study of the reduction of 1-fluoro-2,2-diphenyl-1-methylcyclopropane.[6]

Chart II
Reduction of 2,2-Diphenyl-1-methylcyclopropyl Isocyanide



Reductive cleavage of **13** yields **14**, the ring-opened carbanion, which is in equilibrium with the cyclic imino carbanion **15**. This assumption of a reversible α addition of the diphenyl carbanion to the isocyanide function is

supported by the work of Gerhart and Schöllkopf,[7] who found that the lithium oxazoline **16** is in equilibrium with the ring-opened **17** (eq 6). This reversibility was also ob-



16 **17** (6)

served by Meyers and Collington.[8] Further reduction of **14** and **15** would give the observed products 1,1-diphenylbutane (**10**) and the pyrrolidine **11**. The small amount of the cyclopropane **5** could be accounted for by the alternate pathway through the radical anion **12**. It should be noted that in Chart II the α-addition step serves as a means of trapping the intermediate **14**, which could not have otherwise been identified.

Experimental Section[9]

Reaction of 2,2-Diphenyl-1-methylcyclopropyllithium with 1,1,3,3-Tetramethylbutyl Isocyanide (TMBI). To a stirred solution of 1.22 g (0.0043 mol) of 2,2-diphenyl-1-methylcyclopropyl bromide in 40 ml of ether was added 0.0049 mol of sec-butyllithium (in hexane) at 0°. After stirring for an additional 15 min, the temperature was lowered to −10° and 0.68 g (0.0049 mol) of TMBI[10] was added. The reaction mixture was stirred for 18 hr, followed by addition of 0.5 ml of methanol. The mixture was taken up in ether, extracted with water, and dried over sodium sulfate. Evaporation yielded in oil (1.52 g) which was hydrolyzed in dilute hydrochloric acid–tetrahydrofuran. The mixture was then taken up in ether and washed with water and sodium carbonate solution, and vpc analysis (SE-33) of this solution showed four components, corresponding to 1,1-diphenyl-2-methylcyclopropane (44%), 2,2-diphenyl-4-methylcyclobutanone (46%), 2,2-diphenyl-1-methylcyclopropyl bromide (6%), and 3-methyl-5,5-diphenyldihydrofuran (4%), which were identified by peak enhancement with authentic materials.

Lithium Metal Reduction of (*R*)-(−)-2,2-Diphenyl-1-methylcyclopropyl Isocyanide. A mixture of 2.5 g of lithium dispersion (30% in wax, fine mesh) was washed with hexane and then with portions of THF under argon[11] so that only fine particles of clean lithium remained floating over the clear solvent. The solvent was drained and the lithium was washed into the reaction vessel (containing ground glass and a polyethylene-coated magnetic bar) with 30 ml of DME. The surface of the lithium particles was polished by stirring the suspension vigorously at 25° for 2 hr; then at a temperature of −10°, 0.395 g of the optically pure cyclopropyl isocyanide (powder) was added. After 10 min the deep red solution was decanted from the unused lithium to a flask of cold methanol. The reaction mixture was taken up into ether and washed several times with water. The ether layer was dried (sodium sulfate) and then concentrated to an orange paste: ir (neat) 1720–1620 (w, broad) 1374 (w), 1355 (w), 692 (s), 671 cm^{-1} (s); nmr (CCl_4) δ 0.8–1.4 (m, broad), 1.83 (s), 2.6 (m), 2.94 (d, J = 7 Hz, CH_2CH), 4.44 (t, J = 7 Hz, CH_2CH), 7.03 (s, aromatic), 7.16 (s, aromatic); mass spectrum m/e 441 (parent). The orange paste was hydrolyzed with dilute hydrochloric acid in tetrahydrofuran, and the products were extracted into ether, dried over anhydrous sodium sulfate, and evaporated to yield 0.381 g of an oil. Vpc analysis (15% SE-33 on 80/100 Chromosorb P, AW) showed three major products: **2**, **5** [(*R*)-(+)-2,2-diphenyl-1-methylcyclopropane], and **6**. The hydrocarbon **5** was identified by comparison with the ir and nmr spectra of the authentic material and by vpc peak enhancement (20% EGIP on 80/100 Chromasorb P, AW), $[\alpha]^{25}_{5461}$ +18.0 ± 0.5°. The ketone **6** showed the following properties: ir (CCl_4) 1720 cm^{-1} (s) (lit.[11] 1715 cm^{-1}); nmr ($CDCl_3$) δ 2.06 (s, 3, CH_3), 3.20 (d, 2, J = 7.5 Hz, CH_2), 4.71 (t, 1, J = 7.5 Hz, CH), 7.42 (s, 10, aromatic); 2,4-DNP mp 173–175° (lit.[12] mp 174–175°). The cyclobutane **2** showed the following properties: ir (CCl_4) 1783 (s), 1494 (m), 1450 (m), 692 cm^{-1} (s); nmr ($CDCl_3$) δ 1.32 (d, 3, J = 7 Hz, CH_3), 2.37 (m, 1, J_{AB} = 10.5, J_{AX} = 8 Hz, HCH), 3.09 (m, 1, J_{AB} = 10.5, J_{BX} = 10.5 Hz, HCH), 3.32 (m, 1, CH), 7.0–7.5 (m, 10, aromatic); *ir irradiation at δ 1.32, 3.32 (m, J_{AX} = 8, J_{BX}* = 10.5 Hz); irradiation at δ 3.32, 2.37 (d, J_{AB} = 10.5 Hz); mass spectrum m/e (calcd mass) 235.1199 (calcd for $C_{17}H_{16}O$, 236.1200), 237.1219 (calcd for $C_{16}{}^{13}CH_{16}O$, 237.1234), 208.1274 (calcd for $C_{16}H_{16}$, 208.1292), 181.1020 (calcd for $C_{14}H_{13}$, 181.1017), 166.0778 (calcd for $C_{13}H_{10}$, 166.0782); 2,4-DNP mp 207–208°.

Addition of 2,2-Diphenyl-1-methylcyclopropyllithium to 2,2-Diphenyl-1-methylcyclopropyl Isocyanide. From 1.2 g (0.0042 mol) of 1-bromo-2,2-diphenyl-1-methylcyclopropane a solution of the cyclopropyllithium was prepared in 30 ml of ether[13] under an argon atmosphere. The cyclopropyllithium solution was then filtered into a 60-ml THF solution (−10°) of 0.671 g (0.0028 mol) of 2,2-diphenyl-1-methylcyclopropyl isocyanide. The mixture was stirred for 1 hr, quenched with methanol, and washed with water. The organic layer was dried (sodium sulfate) and evaporated to a viscous oil. The oil was dissolved into 80 ml of hexane with heating. Upon cooling, the unreacted isocyanide separated as crystals. The hexane solution was decanted, and the crystals were dried, 0.56 g, mp 115–123°, ir ($CHCl_3$) 2240 cm^{-1} (s). The hexane solution was evaporated, the concentrate was hydrolyzed in dilute hydrochloric acid–tetrahydrofuran solution for 20 min and taken up in ether, and the ether was washed several times with water. After drying (sodium sulfate), the ether solution was concentrated yielding 0.246 g of an oil. Vpc analysis of the oil (SE-33, silastic LS-40) gave the following composition: 2,2-diphenyl-4-methylcyclobutanone (17%), 4,4-diphenylbutanone (15%), 1-bromo-2,2-diphenyl-1-methylcyclopropane (47% together with some 2,2-diphenyl-1-methylenecyclopropane as impurity).

Acidic Rearrangement of 2,2-Diphenyl-1-methylcyclopropanecarboxaldehyde. To a solution of 0.82 g of 2,2-diphenyl-1-methylcyclopropanecarboxaldehyde[14] in 20 ml of tetrahydrofuran was added 0.5 ml of concentrated sulfuric acid at 25°. The mixture was swirled and left to stand overnight in a stoppered vessel. The contents were then poured into water (0°) and extracted. The ether layer was dried over sodium sulfate and then concentrated to give 0.81 g of a viscous oil: ir (neat) 2930 (m), 1487 (m), 1444 (m), 1378 (m), 1004 (s), 1694 cm^{-1} (s); nmr (CCl_4) δ 1.53 (s, 3, CH_3), 3.16 (s, 2, CH_2), 6.14 (s, 1, C=CH), 7.0–7.4 (m, 10, aromatic); mass spectrum m/e (calcd mass) 236.1208 (calcd for $C_{17}H_{16}$, 226.1200).

Sodium Metal Reduction of 2,2-Diphenyl-1-methylcyclopropyl Isocyanide in Liquid Ammonia. An 8% sodium in liquid ammonia solution (45 ml) was prepared according to the procedure of Pierce and Walborsky.[15] To this solution was added 0.2 g of the isocyanide with stirring. The mixture was then cooled with a Dry Ice–acetone bath as 20 ml of saturated ammonium chloride solution was added dropwise. After addition of hexane, the ammonia was evaporated. The contents of the reaction vessel were separated, and the hexane layer was washed with dilute hydrochloric acid and dried over magnesium sulfate. Evaporation of the solvent gave 0.076 g of a hydrocarbon mixture which, from vpc analysis (20% EGIP on 80/100 Chromasorb P, AW) by peak enhancement with authentic materials was composed of 1,1-diphenyl-2-methylpropane (0.4%). The acidic layer was neutralized with sodium hydroxide solution (0°) yielding an amine which was taken up in ether and dried over sodium sulfate. Evaporation gave 3,3-diphenyl-5-methylpyrrolidine (0.015 g): ir (neat) 3320 (broad), 1491 (s), 1444 (s), 1370 (m), 1028 (m), 689 cm^{-1} (s); nmr (CCl_4) δ 1.04 (d, 3, J = 6 Hz, CH_3CH), 1.59 (s, 1, NH), 1.86 (q, 1, J_{ab} = 12, J_{ax} = 9 Hz, HCHCH), 2.50 (q, 1, J_{ab} = 12, J_{bx} = 6 Hz, HCHCH), 2.80–3.65 (m, 3), 6.99 (s, 10, aromatic); nmr (addition of D_2O) δ 1.59 (disappearance of singlet NH), irradiation at 1.04, 3.32 (q, J_{ax} = 9, J_{bx} = 6 Hz, $HCHCHCH_3$), 3.41 (d, $J_{a'b'}$ = 11.5 Hz, H'CH'), 3.66 (d, $J_{a'b'}$ = 11.5 Hz, H'CH'); mass spectrum m/e (calcd mass) 238.1571 (calcd for $C_{16}{}^{13}CH_{19}N$, 238.1550), 237,1517 (calcd for $C_{17}H_{19}N$, 237.1517), 193.1026 (calcd for $C_{15}H_{13}$, 193.1017), 167.0868 (calcd for $C_{13}H_{11}$, 167.1860), 133.0898 (calcd for $C_9H_{11}N$, 133.0890).

1-(*p*-Nitrobenzoyl)-3,3-diphenyl-5-methylpyrrolidine. The above 3,3-diphenyl-5-methylpyrrolidine was treated with *p*-nitrobenzoyl chloride in the usual manner: mp 146.5–148°; ir ($CHCl_3$) 2995 (m), 1361 (s), 1600 (s), 1524 (s), 1494 (m), 1351 cm^{-1} (s); nmr ($CHCl_3$) δ 0.99 (d, 0.25, J = 6 Hz, CH_3CH) and 1.48 (d, 0.75, J = 6 Hz, CH_3CH), 2.30 (q, 1, J_{ab} = 13, J_{ax} = 10 Hz, HCHCH), 3.07 (q, 1, J_{ab} = 13, J_{bx} = 7 Hz, HCHCH), 3.5–4.5 (m, 3), 6.9–7.5 (m, 10, Ph_2C), 7.65 (d, 2, J = 8.6 Hz, 2,6-H), 8.24 (d, 2, J = 8.6 Hz, 3,5-H).

Anal. Calcd for $C_{24}H_{22}N_2O_3$: C, 74.59; H, 5.74; N, 7.25. Found: C, 74.63; H, 5.77; N, 7.25.

Registry No.—**1**, 50259-68-2; **2**, 50259-69-3; **2** 2,4-dinitrophenylhydrazone, 50259-70-6; **3**, 50259-71-7; **4**, 32528-88-4; **5**, 17413-48-8; **6**, 5409-60-9; **11**, 50259-75-1; 1-(*p*-nitrobenzoyl)-3,3-diphenyl-5-methylpyrrolidine, 50259-76-2.

References and Notes

(1) The support of this work by grants from the National Science Foundation, a Public Health Service Grant No. 04065 from the National Cancer Institute, is gratefully acknowledged.
(2) H. M. Walborsky and G. E. Niznik, *J. Amer. Chem. Soc.*, **91**, 7778 (1969).
(3) H. M. Walborsky, W. H. Morrison, III, and G. E. Niznik, *J. Amer. Chem. Soc.*, **92**, 6676 (1970).
(4) I. Ugi and F. Bodeshein, *Chem. Ber.*, **94**, 1157 (1961); W. Buchner and R. Dufaux, *Helv. Chim. Acta*, **49**, 1145 (1966).
(5) (a) H. M. Walborsky and A. E. Young, *J. Amer. Chem. Soc.*, **86**, 3288 (1964); (b) H. M. Walborsky, F. P. Johnson, and J. B. Pierce, *ibid.*, **90**, 5222 (1968), and references cited therein.
(6) E. J. Powers, Dissertation, The Florida State University, 1969.
(7) F. Gerhart and U. Schöllkopf, *Tetrahedron Lett.*, 6231 (1968).
(8) A. I. Meyers and E. W. Collington, *J. Amer. Chem. Soc.*, **92**, 6677 (1970).
(9) All melting points are uncorrected. Rotations at the 5461-Å mercury line were measured on a Bendix-Ericson Model 987 ETL/NPL polarimeter.
(10) G. E. Niznik, W. H. Morrison, III, and H. M. Walborsky, *Org. Syn.*, **51**, 31 (1972).
(11) The apparatus must be so designed such that all operations can be performed under a total argon atmosphere.
(12) H. O. House, D. D. Traficanti, and R. A. Evans, *J. Org. Chem.*, **28**, 353 (1963).
(13) H. M. Walborsky and M. S. Aronoff, *J. Organometal. Chem.*, **51**, 55 (1973).
(14) H. M. Walborsky and L. E. Allen, *J. Amer. Chem. Soc.*, **93**, 5465 (1971).
(15) H. M. Walborsky, F. P. Johnson, and J. B. Pierce, *J. Amer. Chem. Soc.*, **90**, 5222 (1968).

Isocyanides. Dissociation of Metallo Aldimines

M. P. Periasamy and H. M. Walborsky*

Department of Chemistry, Florida State University, Tallahassee, Florida 32306

Received September 10, 1973

Metallo aldimines were prepared by the addition of organolithium reagents to *tert*-butyl isocyanide, 1,1,3,3-tetramethylbutyl isocyanide, 2-phenyl-2-butyl isocyanide, and triphenylmethyl isocyanide. The reactions of organolithium reagents, Grignard reagents, and organocopper reagents with triphenylmethyl isocyanide are discussed in detail. A new synthetic route for the formation of secondary and tertiary nitriles is described as is a simple and convenient method for the preparation of ketones. The lithium aldimines were converted to copper aldimines by treatment with cuprous iodide. Studies on the dissociative nature of metallo aldimines indicated that both relief of steric crowding (steric effect) and formation of stable intermediates (electronic effect) are the driving forces for the dissociation.

Recent reports on the reaction of isocyanides with organometallic reagents have shown that the chemistry of isocyanides can provide new synthetic pathways to a variety of molecules. It has recently been reported[1] that the α addition of an organolithium reagent to 1,1,3,3-tetramethylbutyl isocyanide (TMBI) yields lithium aldimine (1), which can be used for the preparation of aldehydes, ketones, α-keto acids, and α- and β-hydroxy ketones (eq 1).

$$\overset{+}{R}N\equiv\overset{-}{C} + R'Li \longrightarrow RN=C(R')(Li) \quad (1)$$

1

The reactions of α-metalated isocyanides are being investigated by Schöllkopf and others.[2,3] In addition, the synthetic applications of copper–isocyanide complex catalyzed reactions for the preparation of a variety of compounds have been explored by Saegusa.[4]

During the course of investigating the synthetic utility of lithium aldimines it was discovered that certain aldimines dissociated to produce nitriles in very good yields[5] (eq 2). Preliminary investigations indicated that an 88%

$$RN=C(R')(Li) \longrightarrow R'CN + RLi \quad (2)$$

yield of *tert*-butyl cyanide could be achieved by the addition of the *tert*-butyllithium to triphenylmethyl isocyanide (TPMI). However, the use of other lithium reagents produced the corresponding symmetrical ketones which apparently results from the addition of RLi to the nitrile formed (eq 3b).

A detailed study, with an aim of establishing the scope and limitations of this "isocyanide–metal exchange" reaction[5] was undertaken and is the subject of this paper.

Isocyanide–Metal Exchange Reaction. The isocyanide–metal exchange reaction (eq 3a) showed promise as a new method for the preparation of nitriles and ketones. An investigation of the scope and limitation of this reaction was undertaken. The results obtained in Table IV clearly point to triphenylmethyl isocyanide (TPMI) as the isocyanide of choice, and it was therefore selected for our studies.

$$Ph_3CNC + RLi \longrightarrow Ph_3C(Li)N=C(R) \longrightarrow RCN + Ph_3CLi \quad (3a)$$

$$RCN + RLi \longrightarrow RC(NLi)R \xrightarrow{H^+} RC(O)R \quad (3b)$$

Reactions with Organolithium Reagents. The results of the reactions of a representative set of organolithium reagents with TPMI are given in Table I.[5] It is evident that this reaction provides a convenient method for the preparation of symmetrical ketones and hindered nitriles such as *tert*-butyl cyanide in high yield. Unsymmetrical ketones can also be prepared by the simple expediency of first adding 1 equiv of the more hindered lithium reagent to permit the exchange reaction (eq 3a) to occur, followed by the addition of the less hindered lithium reagent. Using this procedure, *tert*-butyl *sec*-butyl ketone was prepared in 83% yield. It is worth mentioning that by careful work-up of the reaction mixture (see Experimental Section) one can isolate the precursor ketimine in excellent yields. For example, di-*tert*-butyl ketimine was obtained in 77% yield.[6] Lithium phenylacetylide, owing to an unfavorable equilibrium, did not add to TPMI.

The associated nature of organolithium reagents[7,8] may increase the probability of the immediate availability of lithium reagents for further addition to the nitrile as it is formed in the reaction. The observation that the yield of nitrile increased on going from primary to tertiary lithium reagent indicates that steric hindrance also becomes an important factor so that α addition of *tert*-butyllithium to TPMI is favored over its addition to the nitrile formed in

Table I
Reactions of Triphenylmethyl Isocyanide with Organolithium Reagents

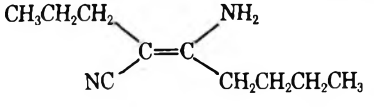
No.	RLi	RLi: Ph_3CNC	Yield,[a] % Nitrile	Yield,[a] % Ketone
1	*n*-Butyl	1:1	8.5	48.5[b]
		2:1	9	59
2	*sec*-Butyl	1:1	14	55[b]
		2:1	24	63
3	*tert*-Butyl	1:1	88	
		2:1	2	75
4	Phenylethynyl	1:1		
5	Cyclopropyl	1:1	1.5	20
6	Phenyl	1:1		93[b]
		2:1		94
7	Mesityl	1:1		14[c]

[a] Yields determined by glpc analysis. [b] Yields based on theoretical yield of ketone. [c] Isolated as ketimine.

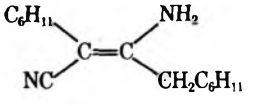
the reaction. The lower yield of dimesityl ketimine is probably due to the steric hindrance experienced in the α addition of the lithium reagent to isonitrile.

Reaction with Grignard Reagents. The availability of organohalides and the ease of preparation of Grignard reagents prompted us to study the reactions of Grignard reagents with TPMI. Although reactions of aromatic and tertiary Grignard reagents were unsuccessful, the results (Table II) with primary and secondary Grignard reactions are significant from a synthetic point of view.

When 1 equiv of *n*-butylmagnesium bromide was treated with TPMI, work-up of the reaction mixture gave neither *n*-valeronitrile nor 5-nonanone. The ir spectrum of the reaction mixture exhibited, in addition to the unreacted isocyanide band at 2140 cm^{-1}, a strong band at 2190 cm^{-1}, absorption in the 3300–3500-cm^{-1} region, and an intense band at 1632 cm^{-1}. These data indicated the presence of an amino and a cyano group in addition to a double bond in conjugation with them. The product was identified as 5-amino-4-cyano-4-nonene (2) by isolation



2



3

and comparison of its ir and nmr spectra with that of an authentic sample prepared in 49% yield by the reaction of *n*-butylmagnesium bromide with *n*-valeronitrile.[9] Conversion of 2 to the known 4-cyano-5-nonanone by mild acid hydrolysis confirmed the structural assignment.

When 2 equiv of *n*-butylmagnesium bromide was treated with 1 equiv of TPMI, depending upon the reaction conditions, a 10–20% yield of *n*-valeronitrile was realized, along with a 50–60% yield of 2. Under similar conditions cyclohexylmethylmagnesium bromide gave a 26% yield of cyclohexylacetonitrile and a 55% yield of 3. It is evident that this reaction, although not satisfactory for the preparation of primary nitriles, provides a facile and convenient synthetic route for making α-cyano ketones or the corresponding precursors in good yields. The mechanism of the condensation that occurs during the reaction of Grignard reagents with primary nitriles has been discussed elsewhere.[10]

As can be seen from Table II, reactions of secondary Grignard reagents with TPMI gave the corresponding nitriles in excellent yields. When Grignard reagent and isocyanide were allowed to react in 1:1 ratio, the yield of nitrile was of the order of 70–95%. The reaction was complete in 5 min with a quantitative yield being obtained when 2 equiv of cyclohexylmagnesium bromide was treated with 1 equiv of TPMI. Similarly, a 98% yield of 2-cyanobutane was obtained from the reaction of 3 equiv of *sec*-butylmagnesium bromide with 2 equiv of TPMI. The important synthetic application of this reaction should be recognized from the fact that ordinarily unsatisfactory yields of nitriles are obtained by the usual SN2 displacement of *sec*-acyclic and cyclic halides by cyanide ions.[11]

However, treatment of *tert*-butylmagnesium bromide with TPMI at 36° for 10 hr gave only a small yield of *tert*-butyl cyanide (~10%). Also, reactions with phenylmagnesium bromide, *p*-methoxyphenylmagnesium bromide, and *p*-methylphenylmagnesium bromide did not yield the corresponding nitrile. In the case of mesitylmagnesium bromide, 2,4,6-trimethylbenzonitrile was obtained in 17% yield, which could be increased to 39% yield when the reaction mixture was refluxed for 18 hr at 65° (THF).

In contrast to the results with lithium reagents (Table I) we note in the case of Grignard reagents that tertiary and aromatic Grignard reagents do not react with TPMI to any appreciable extent. This effect has previously been observed in the reaction of phenylmagnesium bromide with 1,1,3,3-tetramethylbutyl isocyanide (TMBI) and the lack of reactivity was ascribed to an unfavorable equilibrium.[1b,12] A similar situation seems to obtain in the reaction of Grignard reagents with TPMI.

Table II
Reactions of Grignard Reagents with Triphenylmethyl Isocyanide

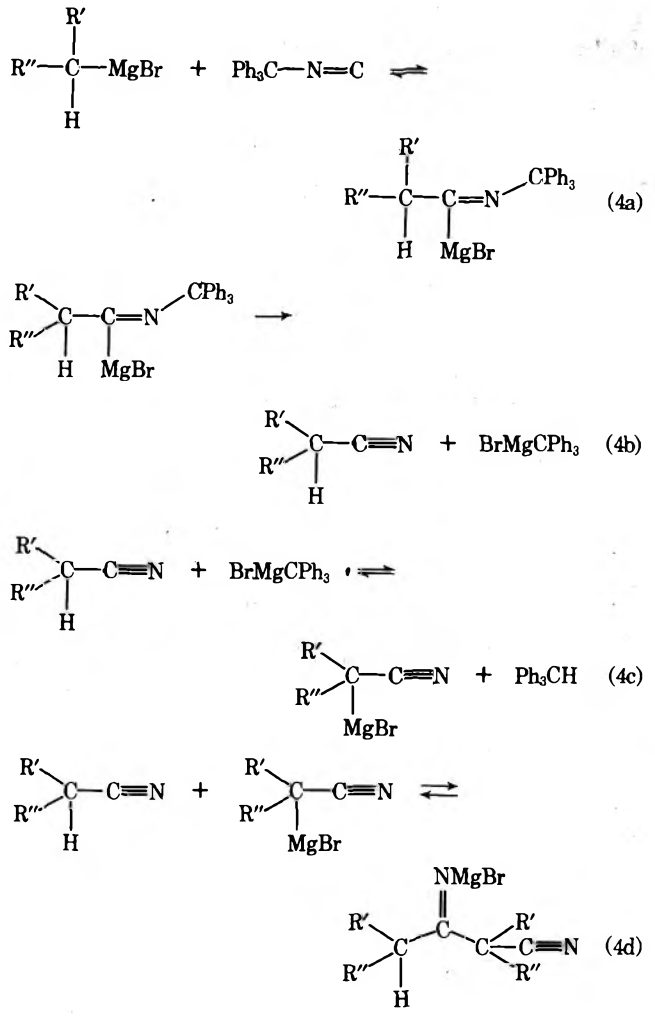
RBr[a]	RMgBr: Ph_3CNC	Yield[b] RCN, %
n-Butyl bromide	1:1	Trace[c]
	2:1	10–20[c]
Cyclohexylmethyl bromide	2:1	26[c]
Benzyl bromide	2:1	78
2-Bromobutane	1:1	70
	3:2	98
2-Bromohexane	1:1	79
Cyclopropyl bromide	1:1	17
	2:1	27
Cyclohexyl bromide	1:1	94
	2:1	100
Cycloheptyl bromide	1:1	70
tert-Butyl bromide	1:1	7–10
Bromobenzene	1:1	Trace
p-Methoxybromobenzene	1:1	Trace
p-Bromotoluene	1:1	Trace
Mesityl bromide	1:1	17

[a] Grignard reagent was prepared by standard procedure and titrated whenever it was necessary. [b] Yields determined by glpc. [c] Other products were isolated. Refer to the discussion section.

Table III
Reactions of Triphenylmethyl Isocyanide with Organocopper Reagents

No.	RCu R		Yields,[a] % RCN	Yields,[a] % Ph_3CH	Conditions: Time, hr	Conditions: Temp, °C
1	*n*-Butyl		38		6.5	34
2	*tert*-Butyl		<5		6.5	34
3	Phenyl		1		6.5	34
	RR'CuLi R	R'				
4	*n*-Butyl	*n*-Butyl	49	62	1	25
5	*n*-Butyl	*n*-Butyl	40	84	6	25
6	*n*-Butyl	*n*-Butyl	17	85	12	10
7	*tert*-Butyl	*tert*-Butyl	31	40	3	36
8	*n*-Butyl	*tert*-Butyl	24[b]	62	0.5	25

[a] Yields determined by glpc. [b] No *tert*-butyl cyanide was formed.

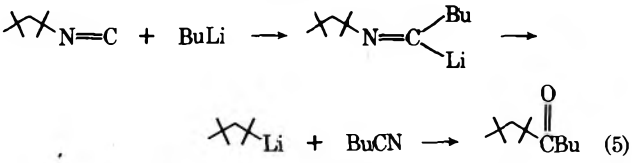


In the case when R″ = H the α-metalated nitrile can undergo further condensation to give products of the type of **2** and **3**. When both R′ and R″ are alkyl groups, one then obtains good yields of nitrile, since the reaction with tritylmagnesium bromide represents a less favorable equilibrium[10b] (eq 4c) and the propensity for condensation is reduced for steric reasons. However, when R′ = phenyl and R″ = H, the equilibrium (eq 4c) will be almost completely to the right, leading to a stable phenylacetonitrile anion, and therefore benzylmagnesium bromide gives good yields of phenylacetonitrile.

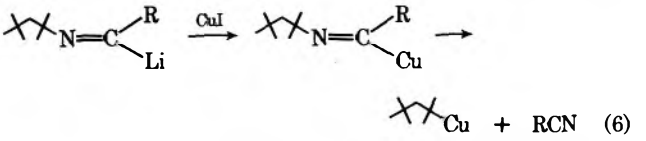
Copper Aldimines. Reaction with Organocopper Reagents. One of the aims in the study of the reaction of organometallics with TPMI was to stop the reaction at the nitrile stage and isolate them free of side products. We have seen that by a judicious choice of organometallic reagent such as tertiary organolithium and secondary Grignard reagents one is able to obtain good yields of the corresponding nitriles. In the case of primary organometallic reagents the nitrile formed in the first step reacted further with both organolithium and Grignard reagents to give ketones and α-cyano ketones, respectively. Since organocopper reagents have been reported to be unreactive toward nitriles,[13] it was felt that the use of these reagents might circumvent the secondary reactions previously encountered. The results of this study are shown in Table III.

The reaction of alkyl- and phenylcopper reagents with TPMI to give nitriles did not proceed to any appreciable extent. The use of lithium dialkylcuprate reagents improved the yield of nitrile somewhat. Although, as anticipated, no ketone or condensation products were formed, the low yields obtained in these reactions mitigate its use as a synthetic tool.

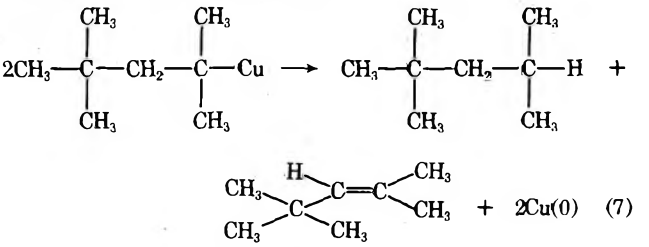
Conversion of Lithium Aldimines to Copper Aldimines. Initial investigations were focused on the effect of the structure of the isonitrile on the course of the reaction. It was hypothesized that the driving force for the dissociation of the lithium aldimine formed by the α addition of *tert*-butyllithium to TPMI was due to the stabilized trityl anion behaving as a good leaving group. It was therefore surprising to observe the formation of 5–10% yield of *n*-butyl 1,1,3,3-tetramethylbutyl ketone, as a minor product, from the addition of *n*-butyllithium to TMBI. Formation of this ketone suggested that the aldimine dissociated to give *n*-butyl cyanide and 1,1,3,3-tetramethylbutyllithium, which upon further reaction furnished the observed ketone (eq 5).



Based on these observations it was felt that the conversion of lithium aldimine to copper aldimine, by the addition of cuprous iodide, should produce 1,1,3,3-tetramethylbutylcopper (eq 6). Since organocopper reagents do not



add to nitriles,[13] one should be able to avoid the formation of ketone and thereby identify the nitrile. Indeed, the copper aldimine obtained from the reaction of cuprous iodide with the lithium aldimine formed from TMBI and *tert*-butyllithium gave a 61% yield of *tert*-butyl cyanide. The formation of 1,1,3,3-tetramethylbutylcopper was also indicated by the identification of its disproportionation products, 2,4,4-trimethylpentane, 2,4,4-trimethyl-2-pentene, and metallic copper (eq 7).



Having established that the lithium or copper aldimines from both triphenylmethyl isocyanide (TPMI) and 1,1,3,3-tetramethylbutyl isocyanide (TMBI) dissociated to produce alkyl cyanides, it became apparent that electronic factors alone could not account for the driving force for this dissociation. Although the former produced the highly delocalized trityl anion, the latter formed a tertiary alkyllithium or alkylcopper reagent, neither of which possess any favorable stabilizing factors. Steric interactions, however, may also be playing an important role in this reaction. To evaluate this possibility a study of the copper aldimine intermediate was undertaken, the results of which are given in Tables IV and V. The copper aldimines were chosen for this investigation since this reaction produces solely nitriles and is not complicated by ketone formation.

The results, shown in Table IV, show the effect of varying the alkyl group (R′ in R′NC) upon the dissociation of metallo aldimines (eq 8). It has been recognized that non-

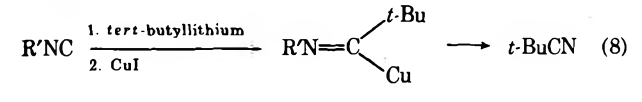


Table IV
Reactions of Copper Aldimines. Effect of Changing R′ Group in Isocyanides

No.	R′NC	RLi	Solvent[a]	Temp, °C	Reaction period, hr	Yield[b] RCN, %
1	*tert*-Butyl	*tert*-Butyl	Et_2O	*f*	2.5	10.5[c]
2	1,1,3,3-Tetramethylbutyl	*tert*-Butyl	Et_2O	*f*	2.5	61[d]
3	1,1,3,3-Tetramethylbutyl	*tert*-Butyl	THF	*f*	2.5	29
4	2-Phenyl-2-butyl	*tert*-Butyl	THF	0	2.5	35
5	Trityl	*tert*-Butyl	THF	−78	0.25	88[e]

[a] *tert*-Butyllithium in pentane or hexane was used. [b] Yields determined by glpc analysis. [c] 43% yield of *N*-*tert*-butyl-2,2-dimethylpropanamide was observed. [d] A small amount of *N*-(1,1,3,3-tetramethylbutyl)-2,2-dimethylpropanamide was noticed. [e] No CuI was added. [f] Room temperature.

Table V
Reactions of Copper Aldimines. Effect of Changing R Group in Organolithium Reagents

No.	R′NC	RLi	Solvent[a]	Temp	Reaction period, hr	RCN	R′NHC(=O)R, % yield[b]
1	1,1,3,3-Tetramethylbutyl	Methyl	Et_2O	*f*	2.5	Trace[c]	<5
2	1,1,3,3-Tetramethylbutyl	*n*-Butyl	Et_2O	*f*	2.5	Trace[d]	27
3	1,1,3,3-Tetramethylbutyl	*sec*-Butyl	Et_2O	*f*	2.5	<2	>90
4	1,1,3,3-Tetramethylbutyl	*tert*-Butyl	Et_2O	*f*	2.5	61	*e*
5	*tert*-Butyl	*tert*-Butyl	Et_2O	*f*	2.5	10.5	43

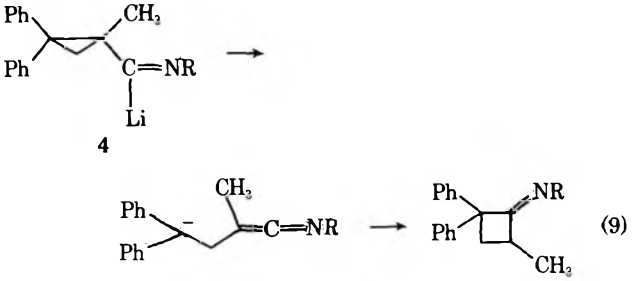
[a] RLi in pentane was used. [b] Yields determined by glpc analysis using authentic sample. [c] Corresponding aldimine was the major product (>90%). [d] Corresponding aldimine was the major product; a 10–12% yield of *n*-butyl 1,1,3,3-tetramethylbutyl ketone was also observed. [e] A small amount of *N*-(1,1,3,3-tetramethylbutyl)-2,2-dimethylpropanamide was detected. [f] Room temperature.

Chart I
***E*-*Z* Isomerization of Metallo Aldimines**

E, R″ = H, Li; *Z*, R″ = Cu — *Z*, R″ = H, Li; *E*, R″ = Cu

bonded interactions between the substituent on nitrogen and the substituent on carbon in imines have a pronounced effect on the *E* to *Z* isomer ratio in these systems.[14] A similar situation should be obtained in the case of the metallo aldimines (Chart I). One should expect that with copper aldimines the most favored configuration would be *Z*, which would place both alkyl groups in a trans relationship to each other. Boyd, *et al.*,[15] have shown that interactions involving the nitrogen lone pair of electrons are important in determining the imine stereochemistry. The localized electron pair or valence shell electron pair repulsion theory assumes that a nonbonding or lone pair of electrons is larger in volume and takes up more space on the surface of an atom than a bonding pair.[16] It seems reasonable that even in their most favored configuration *Z* copper aldimines are inherently sterically crowded systems and will try to minimize their nonbonded interactions, if possible, by dissociation. Under identical conditions copper aldimines obtained by the addition to *tert*-butyl isocyanide and 1,1,3,3-tetramethylbutyl isocyanide (TMBI) gave *tert*-butyl cyanide in 10.5 and 61% yields, respectively. The copper aldimine obtained from TMBI at room temperature in THF rather than ether dissociated to give only a 29% yield of *tert*-butyl cyanide. The lower yield could be attributed to the greater stability of organocopper reagents in THF.[17] However, at 0° in THF, 2-phenyl-2-butyl isocyanide gave a 35% yield of *tert*-butyl cyanide. The observed increase in yield of *tert*-butyl cyanide at a lower temperature (0°) from 2-phenyl-2-butyl isocyanide than from TMBI at room temperature suggests that in addition to a steric factor, electronic effects are also operating through the formation of the benzylic anion.

Moreover, the replacement of both alkyl groups in 2-phenyl-2-butyl isocyanide by two phenyl groups caused the aldimine to dissociate very rapidly (−78°, less than 15 min) largely owing to the stability of the trityl anion produced. These results are consistent with the postulate that both relief of steric strain and the formation of a stable anion are the driving forces for the dissociative ring opening of the lithium aldimine intermediate 4 obtained by the addition of 2,2-diphenyl-1-methylcyclopropyllithium to TMBI (eq 9).[18]

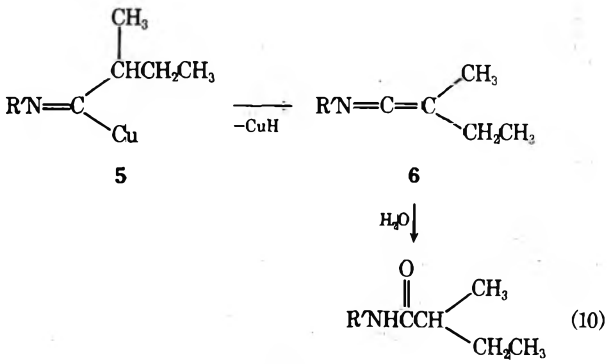


4

R = 1,1,3,3-tetramethylbutyl

The effects of varying the organolithium reagent upon the reaction product composition resulting from the dissociation of metallo aldimines are given in Table V. It should be pointed out that all of the reactions are conducted under an *argon atmosphere*. It is interesting to note that in addition to the formation of corresponding alkylnitriles, in most cases, the formation of an amide was observed to be the major product. From the addition of methyllithium and *n*-butyllithium to TMBI, followed by addition of cuprous iodide, the major product was shown to be the corresponding aldimine and only a trace of alkylnitrile was formed. In the case of *sec*-butyllithium neither the alkylnitrile nor the aldimine was the major product, but a 90% yield of *N*-(1,1,3,3-tetramethylbutyl)-2-methylbutanamide was observed. However, when *tert*-butyllithium was used, the *tert*-butyl cyanide was formed in 61% yield, with *N*-(1,1,3,3-tetramethylbutyl)-2,2-dimethylpropanamide as a minor product.

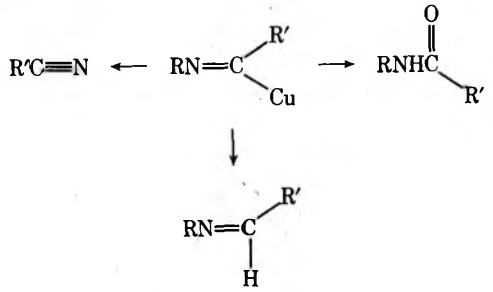
It was noted that the normal work-up (addition of the reaction mixture to aqueous acid) of the copper adimine 5 did not give the corresponding aldimine. This indicated that either the metallo aldimine 5 was stable to acidic conditions or a "ketenimine" (6) was the intermediate which upon addition of water gave the amide in high yield[19] (eq 10). However, since the work-up of the reaction



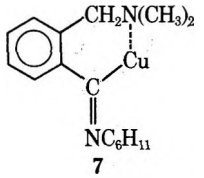
5 6 (10)

R′ = 1,1,3,3-tetramethylbutyl

mixture with D_2O or CH_3OD did not incorporate deuterium at the α position of the amide formed, the possibility of a ketenimine as a viable reaction intermediate was ruled out. It was also observed that the addition of water to the copper aldimine 5 followed by refluxing for 5 hr *under argon* (35°) produced the corresponding aldimine in >90% yield. However, replacing the argon atmosphere by an *oxygen atmosphere* resulted in the formation of amide (49% yield). It therefore appears that the reaction of copper aldimine 5 is very much faster with oxygen than with water and it is this reaction that produces amide. The reaction of a copper aldimine with oxygen to yield amides has also been observed by van Koten and Noltes.[20] It is evident that all of the observed products (Table V), namely aldimine, amide, and nitrile, result from a common copper aldimine intermediate. The question to be answered is why, under identical conditions, these different products are formed in different proportions as one changes R′.

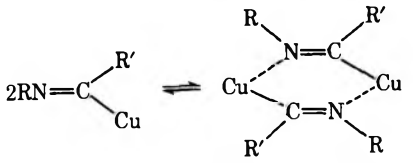


Of significance is the observation of van Koten and Noltes[20] that the copper aldimine 7 is dimeric in benzene



7

solution. They proposed a six-member ring complex formed by intermolecular coordination of two copper aldimines. One might then expect that the metallo aldimines reported in Table V would exist in equilibrium with the dimeric structure and that the position of the equilibrium would be sensitive to the structure of R′ such that when favorable steric conditions exist the equilibrium may be completely over to the dimer (eq 11). As one proceeds from methyl to *sec*-butyl (Table V), it was observed that

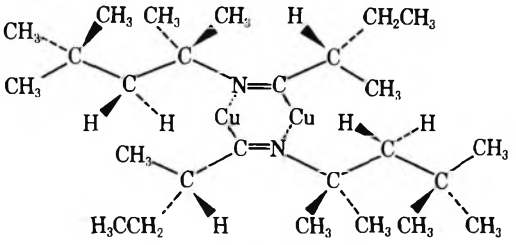


(11)

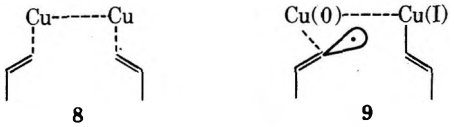
R = 1,1,3,3-tetramethylbutyl; *tert*-butyl
R′ = methyl; *n*-butyl; *sec*-butyl; *tert*-butyl

the yield of aldimine decreased considerably and the formation of amide increased rapidly. It is suggested that as the bulkiness of the organolithium reagent is increased, the stability of the copper aldimine toward hydrolysis increases. A close analysis of the dimer (Chart II) of, for example, the copper aldimine 5 would indicate that the approach of the protonated water molecule (which is solvated) to the Cu–C bond is highly sterically prohibited by the hydrophobic alkyl groups but that its reaction with gaseous oxygen molecule to give amide is not retarded. With a methyl or *n*-butyl group present, the steric crowding around the Cu–C bond is not critical enough to prevent the hydrolysis and hence the aldimine was observed to be the major product. In the case of a *tert*-butyl group the nonbonding interaction between the *tert*-butyl group and the 1,1,3,3-tetramethylbutyl group is very severe and formation of the dimer becomes energetically unfavorable; the copper aldimine would therefore exist mostly as monomer. This conclusion would equally apply to the copper aldimines reported in Table IV. As we have discussed earlier, depending upon the steric and electronic factors, the monomeric copper aldimines dissociated to give nitriles as one of the major components of the products.

Chart II
Dimeric Structure of Copper Aldimine 5



A number of studies have established the thermal disproportionation of alkylcopper(I) reagents to alkane, alkene, and metallic copper (eq 7), with practically no dimerized hydrocarbon product.[21] However, in the case of vinylcopper reagents Whitesides and his coworkers[22] have observed that these reagents decomposed at ambient temperature (4 hr, 25°) to give metallic copper and high yields of dimers with >95% stereospecificity. They concluded that free vinylic radicals are not involved as intermediates and proposed mechanisms which would not involve free radicals. One of the suggestions involved a four-center mechanism and the other a "σ–π" interconversion to an intermediate containing a vinyl radical π bonded to a copper atom cluster, 9. It is seen that the transition state for either of these mechanisms would require the carbon atoms forming the new σ–σ bond (in the product) to face each other. The copper aldimines under discussion did not give any detectable amount of dimeric products. Also, van Koten and Noltes observed that the thermal degradation of 7 in quinoline at 200° yielded the corresponding Schiff's base in 61% yield instead of the expected symmetrical dimer.[20] As we have discussed earlier, the copper aldimines (1, 2, and 3 in Table V) and 7 would be expected to exist in dimeric forms in which the carbon atoms that would form the new σ bond are far away from each other in the six-membered ring structure, and therefore neither of the two proposed transition states (8 and 9) would be



8 9

attained, and therefore no dimeric products would be formed. In the case of copper aldimines existing predominantly in monomeric form, the unfavorable steric crowd-

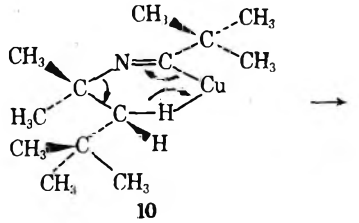
Table VI
Product Distribution from the Decomposition of 1,1,3,3-Tetramethylbutylcopper(I) Reagent

No.	Solvent[a]	Time, min	Yield, %[b] t-BuCN	Alkane[c]	Alkene[d]
1	Et_2O	15	12	2.5	12
2	Et_2O	30	46	18	32
3	*Et_2O*	*480*	*55*	*23*	33
4	THF	150	29	3.7	27.8

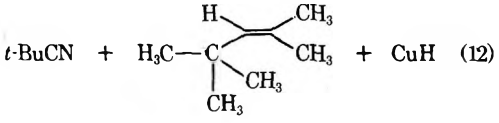
[a] Organolithium in pentane was used. [b] Yields determined by glpc analysis using authentic samples. [c] 2,4,4-Trimethylpentane. [d] 2,4,4-Trimethyl-2-pentene.

ing that would develop in transition states 8 or 9 would be severe enough to prevent the coupling reaction. In these cases an alternate reaction occurs, that of dissociation, due in part to relief of steric strain.

Finally, we would like to comment on the mechanism for the dissociation of copper aldimines to alkylnitriles and alkylcopper. One of the probable mechanisms involves the cleavage of copper aldimines to give alkylnitrile and organocopper. The latter reagent disproportionates to yield equal amounts of alkane, alkene, and metallic copper (eq 6 and 7). However, as can be seen in Table VI, the yield of 2,4,4-trimethyl-2-pentene was higher than that of 2,4,4-trimethylpentane. Moreover, in the decomposition of the 2-phenyl-2-butylcopper intermediate, 2-phenyl-2-butene was formed in about 25–30% higher yield than *sec*-butylbenzene. To account for the increase in olefin yield we would like to suggest that the copper aldimine, besides dissociating to give nitrile and alkylcopper (eq 6), can also dissociate *via* transition state **10** (eq 12) to yield nitrile and olefin.



10



Experimental Section

Melting points were measured with a Mel-Temp apparatus and both melting and boiling points are uncorrected. Infrared spectra were obtained using a Perkin-Elmer Model 257 spectrophotometer. Nuclear magnetic resonance spectra were recorded on a Varian A-60 or Brucker 90-MH spectrophotometer; chemical shifts are reported in parts per million downfield from tetramethylsilane and coupling constants are in hertz. Low-resolution mass spectra were obtained on a Nuclide electron impact mass spectrometer. Glpc analyses were carried out on F & M Model 500 gas chromatograph under reported conditions. Microanalyses were performed by the Beller Laboratories, Gottingen, Germany.

Solvents. Reagent-grade tetrahydrofuran (THF) and diethyl ether were distilled from lithium aluminum hydride under nitrogen and stored over 3A Molecular Sieves. Bulk solvents were distilled before use. Industrial grade dimethylformamide (DMF) was purified by distilling from barium oxide and discarding a forecut.

Reagents. Isocyanides were synthesized using a recent procedure.[23] Cuprous iodide was dried in an oven (120°) for 6 hr and cooled in a desiccator just before use. Organolithium reagents purchased from Foote Minerals Co. were titrated before use.[24] Grignard reagents were prepared using standard procedures and analyzed whenever it was necessary. Established procedures were used to prepare organocopper reagents.[25] All other reagent-grade materials were purified by distillation.

General Procedure for Preparing Metallo Aldimines. The following procedure is typical of compounds reported in Tables IV–VI.

To 2.085 g (15 mmol) of TMBI dissolved in 15 ml of dry ether at room temperature, under an argon atmosphere, was added 15.5 mmol of *tert*-butyllithium (in pentane) over a period of 2–3 min. After stirring for 10 min at room temperature, 3.04 g (16 mmol) of CuI was added and the mixture was stirred for 2.5 hr at ambient temperatures. The mixture was poured onto a mixture of ice and hydrochloric acid, under argon, and extracted with ether after separating inorganic material by filtration. The ether extract was washed with aqueous ammonia, dilute hydrochloric acid, and water, and dried over anhydrous sodium sulfate. Glpc analysis using an authentic sample on a 10 ft × 0.25 in. 10% LS 420 and 5% DEGS on 60/50 AWCP column at 90° indicated that *tert*-butyl cyanide was formed in 61% yield.

Glpc analysis using authentic samples on the above column at 40° showed the yield of 2,4,4-trimethylpentane and 2,4,4-trimethyl-2-pentene to be 18 and 32%, respectively, when the yield of *tert*-butylnitrile was 46% (entry 2, Table III).

Identification of *n*-Butyl 1,1,3,3-Tetramethylbutyl Ketone. *n*-Butyl 1,1,3,3-tetramethylbutyl ketone was identified by ir, nmr, and mass spectral analysis: bp 79–80° (3 mm); ir (CCl_4) 1702 (s) and 1368 cm^{-1}; nmr (CCl_4) δ 0.87 (12, s), 1.11 (6, 2), 1.78–1.11 (4, broad), 1.62 (2, s), 2.42 (2, t, J = 7 Hz); mass spectrum parent ion m/e 198.

Anal. Calcd for $C_{13}H_{26}O$: C, 78.8; H, 13.22. Found: C, 78.76; H, 13.13.

Identification of *N*-(1,1,3,3-Tetramethylbutyl)pentanamide. *N*-(1,1,3,3-tetramethylbutyl)pentanamide was identified by ir, nmr, and mass spectral analysis: bp 108–110° (4 mm); ir (CCl_4) 3440, 3360–3330, 1685 (s), 1508, and 1376 cm^{-1}; nmr (CCl_4) δ 0.99 (12, s), 1.36 (6, s). 1.79 (2, s), 1.78–1.11 (4, broad), 2.09 (2, t, J = 7 Hz), 6.8 (1); mass spectrum m/e 213, 198, 171, 156, 142, 114, 102, 72, 58, 57.

Anal. Calcd for $C_{13}H_{27}NO$: C, 73.19; H, 12.76; O, 7.50. Found: C, 73.20; H, 12.73; O, 7.48.

Identification of *N*-(1,1,3,3-Tetramethylbutyl)-2-methylbutanamide. *N*-(1,1,3,3-Tetramethylbutyl)-2-methylbutanamide was identified by ir, nmr, and mass spectral analysis: mp 86–88°; ir (CCl_4) 3435, 1685 (s), 1505, and 1372 cm^{-1}; nmr (CCl_4) δ 0.86–1.07 (14, m), 1.36 (6, s), 1.72 (3, d, J = 8 Hz), 1.57–2.08 (3, broad), 5.22 (1, broad); mass spectrum m/e 213, 198, 156, 142, 114, 102, 97, 58, 57.

Anal. Calcd for $C_{13}H_{27}NO$: C, 73.19; H, 12.76; N, 6.56. Found: C, 73.33; H, 12.70; N, 6.54.

Identification of *N*-(1,1,3,3-Tetramethylbutyl)-2,2-dimethylpropanamide. *N*-(1,1,3,3-Tetramethylbutyl)-2,2-dimethylpropanamide was identified by ir, nmr, and mass spectral analysis: mp 85–86°; ir (Cl_4) 3440, 1670 (s), 1505, and 1370 cm^{-1}; nmr (CCl_4) δ 1.0 (9, s), 1.10 (9, s), 1.33 (6, s), and 1.71 (2, s); mass spectrum m/e 213, 198, 156, 142, 112, 97, 85, 57, 55.

Anal. Calcd for $C_{13}H_{27}NO$: C, 73.19; H, 12.76; N, 6.56. Found: C, 73.31; H, 12.64; N, 6.63.

General Procedure for the Reaction of Organolithium Reagent with TPMI. The following procedures A and B are typical of reactions run in 1:1 and 2:1 ratios, respectively (Table IV).

A. To a stirred solution of 2.69 g (10 mmol) of TPMI dissolved in 20 ml of dry THF at −78° under a dry argon atmosphere was added 10 mmol of *tert*-butyllithium (in pentane) over a period of 2–3 min. After stirring for 30 min at −78°, the mixture was poured onto an ice-water, extracted with ether, and dried over anhydrous sodium sulfate. Glpc analysis indicated the yield of *tert*-butyl cyanide to be 88%.

B. To a stirred solution of 5.38 g (20 mmol) of TPMI dissolved in 30 ml of dry THF at −78° under an argon atmosphere was added 40 mmol of *tert*-butyllithium (in pentane) over a period of 8–10 min. After stirring for an additional period of 30 min, the mixture was brought to room temperature and stirred for 2 hr. The reaction mixture was worked up as above, and after the ether extract was concentrated, the crude ketimine was refluxed with dilute hydrochloric acid for 2 hr. The ether extraction was concentrated and distilled to give 2.13 g (~75%) of di-*tert*-butyl ketone, bp 150–151°.

Di-*tert*-butylketimine. The above procedure was repeated but omitting the acid hydrolysis step. The reaction mixture was poured into an ice-water mixture and extracted with either. Distillation of the crude reaction product gave 2.18 g (77.4% yield) of di-*tert*-butylketimine:[6] bp 163–163.5°; ir (neat) 1610 and 1372 cm^{-1}; nmr (CCl_4) δ 1.24 (18, s), 0.95 (1, broad); mass spectrum parent ion m/e 141.

Anal. Calcd for $C_9H_{19}N$: C, 76.53; H, 13.56. Found: C, 76.57; H, 13.66.

Identification of Dimesitylketimine. Dimesitylketimine was identified by ir, nmr, and mass spectral analysis: mp 124–125.5°; ir ($CHCl_3$) 3540–3260 (broad), 1620, 1600 (s), 910, and 855 cm^{-1} (s); nmr (CCl_4) δ 2.29 (12, s), 2.44 (6, s), and 9.11 (1, broad); mass spectrum m/e 265.

Anal. Calcd for $C_{19}H_{23}N$: C, 85.98; H, 8.74. Found: C, 85.86; H, 8.76.

General Procedure for the Reaction of Grignard Reagent with TPMI. Primary Grignard Reagent. To a stirred solution of 35 mmol of freshly prepared *n*-butylmagnesium bromide in ether at room temperature and under an argon atmosphere was added 4 g (15 mmol) of TPMI dissolved in dry THF over a period of 2–3 min. The reaction mixture was refluxed for 2 hr, poured onto a mixture of ice–dilute hydrochloric acid, and extracted with ether. Glpc analysis on a 6 ft × 0.25 in. XE-60 column indicated a 10–20% yield of *n*-valeronitrile. Concentration of solution followed by elution through alumina column with a mixture of ether–pentane as eluent gave 0.72 g (58% yield) of 5-amino-4-cyanononene-4 (2) whose spectral properties were identical with that of an authentic sample, prepared as below.

5-Amino-4-cyanononene-4 (2). To 2.9 g (35 mmol) of *n*-valeronitrile dissolved in 5 ml of dry THF at 0° under an argon atmosphere was added 20 mmol of *n*-butylmagnesium bromide over a period of 10 min. The mixture was refluxed for 3 hr and the resin-like material along with solvent was poured onto a dilute hydrochloric acid–ice mixture. The ether extract was washed once with water and twice with saturated sodium chloride solution and dried over anhydrous sodium sulfate. Vacuum distillation of the concentrated crude product gave 1.45 g (49% yield) of pure product: bp 142–143° (5 mm) [lit.[9] bp 125–126° (3 mm)]; ir (CCl_4) 3490, 3390, 3360 (m), 2190 (s), and 1632 cm^{-1} (vs); nmr (CCl_4) δ 4.72 (s, 2, position concentration dependent), 2.35 (t, 2), 1.97 (t, 2), 1.47 (complex, 6), 0.95 (t, 6); mass spectrum parent ion m/e 166.

Hydrolysis of 5-Amino-4-cyanononene-4. An aqueous solution of 2.85 g of 2 in dilute hydrochloric acid was refluxed for 6 hr and evaporation of the ether extract gave about 2.86 g (~100%, crude) of product, which was then distilled: bp 100–101° (5 mm) [lit.[9] bp 127–128° (18 mm)]; ir (CCl_4) 2245 (m), 1728 cm^{-1} (vs); nmr (CCl_4) δ 3.43 (t, 1), 2.72 (t, 2), 1.25–2.0 (complex, 8), 1.06 (t, 6).

Identification of 2-Amino-1-cyano-1,3-dicyclohexylpropene (3). 2-Amino-1-cyano-1,3-dicyclohexylpropene was identified by its ir and nmr analysis: mp 134–136°; ir (CCl_4) 3475, 3380, 2190 (s), 1620 cm^{-1} (vs); nmr ($CDCl_3$) δ 4.11 (2, broad), 2.27 (2, d, J = 7 Hz), 2–2.26 (1, t, overlapping with cyclohexyl protons), 1–2 (21, complex).

Anal. Calcd for $C_{16}H_{26}N_2$: C, 78.0; H, 10.54. Found: C, 77.7; H, 10.62.

Secondary Grignard Reagent. To 35 mmol of cyclohexylmagnesium bromide in ether at 0° under an argon atmosphere was added 8.07 g (30 mmol) of TPMI dissolved in 40 ml of dry THF. The mixture was refluxed for 1.5 hr, poured onto an ice–dilute hydrochloric acid mixture, and extracted with ether. The ether extract was washed with water, saturated with sodium chloride solution, and dried over anhydrous sodium sulfate. Glpc analysis in a 10 ft × 0.25 in. 10% LS 420 and 5% DEGS and 60/50 AWCP column showed that cyclohexyl cyanide was formed in 94% yield.

After removing the solvents the mixture was distilled to give 2.55 g (78% yield) of cyclohexylnitrile, bp 44–45° (4 mm) [lit.[26] bp 72–75° (12 mm)], ir (CCl_4) 2248 cm^{-1} (m).

Tertiary Grignard Reagent. To 15 mmol of *tert*-butylmagnesium bromide in ether at room temperature under an argon atmosphere was added 2.5 g (10 mmol) of TPMI dissolved in 15 ml of dry THF over a period of about 90 sec. The mixture was refluxed for 2 hr and poured onto ice–dilute hydrochloric acid mixture. Glpc analysis of the ether extract showed that *tert*-butyl cyanide was formed in 6–7% yield. The unreacted trityl isocyanide was recovered.

In a like manner, the Grignard reagent was prepared in THF and the reaction mixture was refluxed for 10 hr. Infrared analysis of the reaction product indicated the absence of TPMI. The major product was observed to be triphenylmethyl cyanide with less than 5% yield of *tert*-butyl cyanide.

Aromatic Grignard Reagent. To 2.42 g (9 mmol) of TPMI dissolved in 10 ml of dry THF at 0° under an argon atmosphere was added 9 mmol of mesitylmagnesium bromide over a period of 5 min. After refluxing for 2 hr, the reaction mixture was worked up as usual. Glpc analysis using an authentic sample indicated the yield of 2,4,6-trimethylbenzonitrile to be 17%.

The above reaction was repeated but refluxed for 18 hr before work-up. The yield of 2,4,6-trimethylbenzonitrile was observed to be 39%.

General Procedure for the Reaction of Organocopper Reagent with TPMI. Reaction of *n*-Butylcopper with TPMI. To 3.82 g (20 mmol) of dry cuprous iodide in 15 ml of dry ether at −20° under an argon atmosphere was added 20 mmol of *n*-butyllithium (in hexane) drop by drop over a period of 20–25 min, giving a black solution. After the cold bath was removed, 2.69 g (10 mmol) of TPMI dissolved in 20 ml of dry THF was added over a period of 1–2 min at a rate such that the temperature of the mixture was brought to 25°. The mixture was refluxed for 6.5 hr and then poured onto cold water under an argon atmosphere. After the inorganic residue was filtered off, the ether extract was washed with ammonia solution followed by dilute acid and finally with water. Glpc analysis of the dried (Na_2SO_4) reaction mixture indicated a 38% yield of *n*-valeronitrile. After solvents were removed, the mixture was refluxed for 3 hr with dilute hydrochloric acid and extracted with ether. Glpc analysis indicated <2% yield of 5-nonanone.

Reaction of Lithium Di-*n*-butyl Cuprate with TPMI. To an ether solution of 25 mmol of *n*-butyllithium (in pentane) and 2.38 g (10.5 mmol) of cuprous iodide was added 2.69 g (10 mmol) of TPMI in 20 ml of THF. The reaction was stirred for 6 hr at 25° and worked up in the usual manner. Glpc analysis on a 10 ft × 0.25 in. 10% LS 420 and 5% DEGS and 60/50 AWCP column indicated a 40% yield of *n*-valeronitrile. The yield of triphenylmethane was found to be 84% from glpc analysis on a 4 ft × 0.25 in. SF-96 column. The inorganic residue was stirred with 20 ml of THF for 30 min over a steam bath. Filtration followed by addition of petroleum ether (bp 30–60°) gave <0.1 g of triphenylcarbinol, mp 161–163°; ir was found to be identical with that of an authentic sample.

Acknowledgment. The support of this work by Public Health Service Grant No. 04065 from the National Cancer Institute is gratefully acknowledged.

Registry No.—**2,** 49689-62-5; **3,** 49633-70-7; TPMI, 1600-49-3; TMBI, 14542-93-9; *n*-butyl 1,1,3,3-tetramethylbutyl ketone, 49633-72-9; *N*-(1,1,3,3-tetramethylbutyl)pentanamide, 49633-73-0; *N*-(1,1,3,3-tetramethylbutyl)-2-methylbutanamide, 49633-74-1; *N*-(1,1,3,3-tetramethylbutyl)-2,2-dimethylpropanamide, 49633-75-2; di-*tert*-butyl ketone, 815-24-7; di-*tert*-butylketimine, 29097-52-7; dimesitylketimine, 49633-78-5; 4-cyano-5-nonanone, 49633-79-6.

References and Notes

(1) (a) H. M. Walborsky and G. E. Niznik, *J. Amer. Chem. Soc.*, **91,** 7778 (1969); (b) H. M. Walborsky, W. H. Morrison, III, and G. E. Niznik, *ibid.*, **92,** 6675 (1970).
(2) (a) U. Schöllkopf, D. Hoppe, and R. Jentsch, *Angew. Chem., Int. Ed. Engl.*, **10,** 331 (1971); (b) U. Schollkopf and R. Schroder, *Angew. Chem.*, **84,** 289 (1972); (c) U. Schollkopf and P. H. Porsch, *Angew. Chem., Int. Ed. Engl.*, **11,** 429 (1972); (d) U. Schöllkopf and R. Jentsch, *ibid.*, **12,** 323 (1973).
(3) (a) A. M. van Leusen and H. E. van Gennep, *Tetrahedron Lett.*, 627 (1973); (b) O. H. Oldenziel and A. M. van Leusen, *ibid.*, 1357 (1973).
(4) (a) T. Saegusa, Y. Ito, H. Kinoshita, and S. Tomita, *J. Org. Chem.*, **36,** 3316 (1971); (b) T. Saegusa, Y. Ito, and S. Tomita, *J. Amer. Chem. Soc.*, **93,** 5656 (1971); (c) T. Saegusa, K. Yonezawa, and Y. Ito, *Syn. Commun.*, **2,** 431 (1972); (d) T. Saegusa, I. Murase, and Y. Ito, *J. Org. Chem.*, **38,** 1753 (1973); (e) Y. Ito, Y. Inubushi, M. Zenbayashi, S. Tomita, and T. Saegusa, *J. Amer. Chem. Soc.*, **95,** 4447 (1973).
(5) H. M. Walborsky, G. E. Niznik, and M. P. Periasamy, *Tetrahedron Lett.*, 4965 (1971).
(6) H. D. Hartzler, *J. Amer. Chem. Soc.*, **93,** 4527 (1971).
(7) J. B. Smart, R. Hogan, P. A. Scherr, L. Ferrier, and J. P. Oliver, *J. Amer. Chem. Soc.*, **94,** 8371 (1972), and references cited therein.
(8) A. M. Rodioniv, D. M. Shigorin, T. V. Talalaeva, G. V. Tsareva, and K. A. Kocheshkov, *Russ. J. Phys. Chem.*, **40,** 1217 (1966).
(9) R. H. Wiley and H. Adkins, *J. Amer. Chem. Soc.*, **60,** 914 (1938).
(10) (a) H. Theis, H. Schonenberger, and P. K. Qasba, *Arch. Pharm. (Weinheim)*, **302,** 161, 168 (1969); (b) A. Kirrmann and J. Rabesiaka, *Bull. Soc. Chim. Fr.*, 4908 (1968).
(11) (a) R. A. Smiley and C. Arnold, *J. Org. Chem.*, **25,** 257 (1960); (b) L. Friedman and H. Schechter, *ibid.*, **25,** 877 (1960).
(12) G. E. Niznik, W. H. Morrison, III, and H. M. Walborsky, *J. Org. Chem.*, **39,** 600 (1974).
(13) J. F. Normant and M. Bourgain, unpublished results as cited in J. F. Normant, *Synthesis*, 63 (1972), ref 19.
(14) (a) J. Hine and C. Y. Yeh, *J. Amer. Chem. Soc.*, **89,** 2699 (1967); (b) D. A. Nelson and R. L. Atkins, *Tetrahedron Lett.*, 5197 (1967); (c) E. Melendez, *et al.*, *An. Quim.*, **66,** 87 (1970).
(15) J. Bjorgo, D. R. Boyd, C. G. Watson, and W. B. Jebbinbs, *Tetrahedron Lett.*, 1747 (1972), and references cited therein.
(16) R. J. Gillespie, *J. Chem. Educ.*, **47,** 18 (1970).

(17) K. Wada, M. Tamura, and J. Kochi, J. Amer. Chem. Soc., 92, 6656 (1970).
(18) G. E. Niznik and H. M. Walborsky, J. Org. Chem., 39, 608 (1974).
(19) For a similar reaction refer to H. Ulrich, "The Chemistry of Imidoyl Halides," Plenum Press, New York, N. Y., 1968, Chapter 3.
(20) G. van Koten and J. G. Noltes, Chem. Commun., 59 (1972).
(21) (a) G. M. Whitesides, E. R. Stedronsky, C. P. Casey, and J. San Fillippo, Jr., J. Amer. Chem. Soc., 92, 1426 (1970); (b) M. Tamura and J. Kochi, ibid., 93, 1485 (1971).
(22) G. M. Whitesides, C. P. Casey, and J. K. Krieger, J. Amer. Chem. Soc., 93, 1379 (1971).
(23) H. M. Walborsky and G. E. Niznik, J. Org. Chem., 37, 187 (1972).
(24) R. L. Epplex and J. A. Dixon, J. Organometal. Chem., 8, 176 (1967).
(25) H. Gilman, R. G. Jones, and L. A. Woods, J. Org. Chem., 17, 1630 (1952).
(26) C. H. Tilford, L. A. Doerle, M. G. van Campen, Jr., and R. S. Shelton, J. Amer. Chem. Soc., 71, 1705 (1949).

The Chemistry of 2-Chloromethyl-5,6-dihydro-1,3-oxazines. Grignard Coupling and Metalation Studies. A Synthesis of α-Chloro Aldehydes and Arylacetic Acids[1]

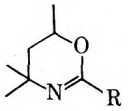
G. Ray Malone and A. I. Meyers*[2]

Department of Chemistry, Wayne State University, Detroit, Michigan 48202

Received August 31, 1973

Treatment of the 2-chloromethyloxazine **2** with lithium hexamethylsilazane produces the α-chloromethyloxazine carbanion **12** which, upon alkylation, leads to the elaborated oxazine. The latter may be reduced and hydrolyzed to α-chloro aldehydes or directly hydrolyzed to α-chlorocarboxylic acids. Studies on **2** using aryl Grignard reagents gave satisfactory yields of coupling products which ultimately led to arylacetic acids. However, alkyl Grignard or lithium reagents led to an array of products, indicating that this process would not be synthetically useful.

The synthetic utility of the 2-substituted 5,6-dihydro-1,3-oxazine **1** has been well established in previous reports from these laboratories. A series of substituted acetaldehydes has been prepared from the 2-methyl-, 2-benzyl-, and 2-carboethoxyoxazines **1a**,[3] while α,β-disubstituted propionaldehydes have been obtained from the 2-vinyl system **1b**.[3] Use of the 2-isopropyl- or other 2-isoalkyloxazines **1c** served as precursors to α-(quaternary carbon) ketones,[4] whereas the 2-alkylidene derivatives **1d** led to additional α-branched ketones.[1] It, therefore, becomes evident that the nature of the R moiety in the oxazine **1** imparts considerable versatility to its synthetic usefulness and further studies were undertaken to introduce other substituents of varied structure. One such substituent chosen for its potential utility was the chloromethyl group, **2**. This derivative was readily prepared by condensing chloroacetonitrile and 2-methyl-2,4-pentanediol in cold sulfuric acid according to previously described procedures for obtaining these oxazines.[3]

DHOR ≡ 

1a, R = CH_3; CH_2Ph; CO_2Et
1b, R = $CH{=}CH_2$
1c, R = $CHMe_2$
1d, R = $MeCH{=}CH_2$, $PhCH{=}CH_2$
2, R = CH_2Cl

Results and Discussion

Reaction of 2-Chloromethyloxazine (2) with Grignard Reagents. A study to determine whether it was feasible to couple the 2-chloromethyloxazine with Grignard reagents was initiated solely for the purpose of obtaining elaborated oxazines **3** that would then serve as precursors to the substituted acetaldehydes **4**. If successful, this sequence would possess three distinct advantages: (a) eliminate the use of *n*-butyllithium to form the anion **5**; (b) provide an alternative route to the elaborated oxazine **3**; and (c) overcome the lack of nucleophilic displacement of aryl halides with **5** and provide a method for arriving at arylmethyl oxazines **6** (and ultimately to arylacetaldehydes). By placing an electrophilic site on the oxazine and utilizing organometallics as the nucleophilic moiety, the roles of the reagents would essentially be reversed from the original oxazine-aldehyde synthesis.

$$\underset{\mathbf{2}}{DHOCH_2Cl} + RMgX \longrightarrow \underset{\mathbf{3}}{DHOCH_2R} \longrightarrow \underset{\mathbf{4}}{O{=}CHCH_2R}$$

$$\underset{\mathbf{5}}{DHOCH_2Li} + ArX \not\longrightarrow \underset{\mathbf{6}}{DHOCH_2Ar}$$

The reactions of **2** with methyl, ethyl, and phenyl Grignard reagents, as suitable models, were surveyed under a variety of conditions. Treatment of **2** with 1.0 equiv of the above Grignard reagents led mainly to recovery of starting materials (~70–80%) when either ether or THF was used as solvent. This implies that a complex between **2** and the Grignard was formed initially without any subsequent transformation. The possibility that proton abstraction from **2** occurred, producing the anion **7**, was precluded when the recovered chloromethyloxazine was found to be devoid of deuterium upon quenching in deuterium oxide.

$$\underset{\mathbf{2}}{DHOCH_2Cl} + RMgX \not\longrightarrow \underset{\mathbf{7}}{DHOCH(Cl)MgX^+} \xrightarrow{D_2O} \not\longrightarrow DHOCHDCl$$

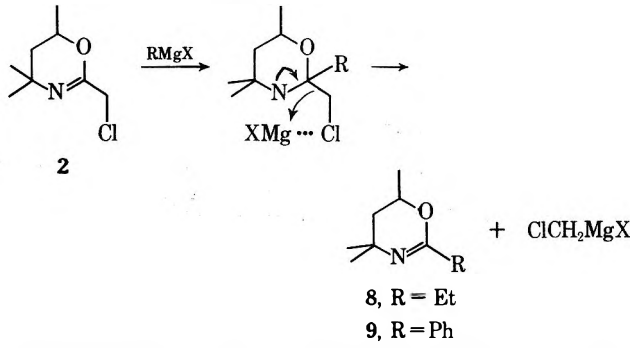
When 2.5 equiv of Grignard reagent was added to **2** and the ethereal solution was heated overnight at reflux, mixtures of products were obtained (Table I). In all instances coupling products were obtained in poor to moderate yields (10–30%) accompanied by starting material and intractable tars. For the reaction of **2** with ethyl and methyl Grignard, the 2-methyloxazine was found to accompany the coupling products. These probably arose from "functional exchange"[5] between **2** and the Grignard reagent prior to quenching. The most interesting product observed was the 2-ethyloxazine **8** from ethyl Grignard and the 2-phenyloxazine **9** from 2-phenyl Grignard. Both of these compounds have been prepared previously[6] and comparison confirmed their identity. Formation of these oxazines may be rationalized by an addition-elimination

Table I
Reaction of RMgX + 2-Chloromethyloxazine (2) in Ether (35°, 16 hr)

Grignard (equiv)	Products[a]		
CH_3MgI (2.5)	$DHOCH_3$ (20%)	$DHOCH_2CH_3$ (20%)	
CH_3CH_2MgBr (2.5)	$DHOCH_3$(20%)	$DHOCH_2CH_3$(5%)	$DHOCH_2CH_3CH_3$ (20%)
C_6H_5MgBr (2.5)	$DHOCH_2Ph$ (30%)	DHOPh (70%)	

[a] Separated by glc (SE-31 on Diatoport S) and collected for structure verification. Unidentifiable materials accounted for 40–60% of the total material balance.

pathway on the chloromethyloxazine **2** producing the chloromethylmagnesium halide. No products derived from this species could be detected. The presence of **8** and **9**

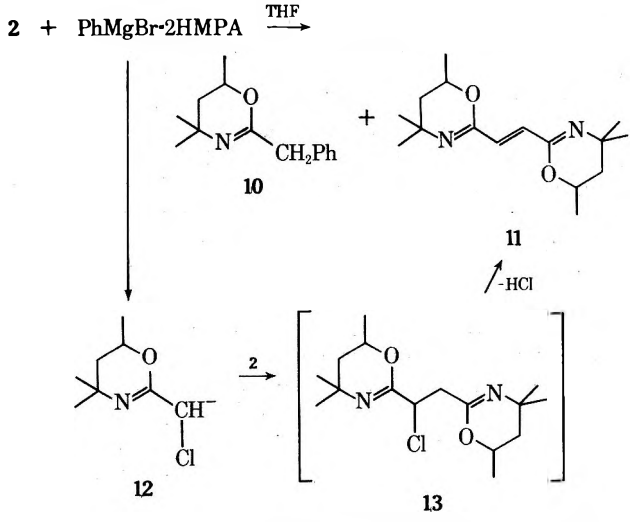


2

8, R = Et
9, R = Ph

was unexpected in view of the fact that the C=N link in oxazines has repeatedly been shown to be inert to Grignard reagents.[3] The presence of the electronegative halogen-containing substituent, however, might render the C=N link in **2** sufficiently electrophilic to allow Grignard addition. These results indicate that direct coupling of Grignard reagents with **2** is not a synthetically feasible process. Changing solvents from ether to THF provided comparable mixtures of products and, thus, proved equally disappointing.

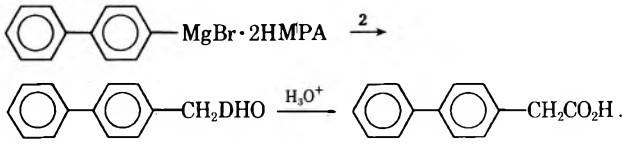
In light of the remarkable solvating properties of hexamethylphosphoramide[7] [HMPA = $(Me_2N)_3PO$] and its effect upon coupling of Grignard reagents with alkyl halides,[8] its use in this study was evaluated. Treatment of **2** with phenylmagnesium bromide in THF previously complexed with 2.0 equiv of HMPA gave the coupling product **10** in 65% yield along with 5% of the 1,2-bis(oxazinyl)ethylene **11** and 12–15% of starting material. The appearance



10 **11** **12** **13**

of the ethylene derivative was not surprising in light of previous studies[9] which showed that Grignard reagents tend to become stronger bases in the presence of HMPA. Thus, **11** would arise from proton abstraction from **2** leading to the anion **12** which displaces choride ion from unreacted **2** forming the bischloro adduct **13**. The latter would be expected to eliminate hydrogen chloride in the presence of the basic medium or upon aqueous work-up. To confirm that **11** does indeed arise from the enhanced base strength of the Grignard reagent, the reaction was repeated using 1:1 THF–HMPA. The large excess of HMPA now present led to an 80% yield of **11** and only traces of the coupled product **10**. When **2** was treated with ethyl or methyl Grignard reagents complexed with 2.0 equiv of HMPA, only **11** was produced. This result is consistent with previous observations[9] that Grignard reagents containing sp^3 carbon bonded to the magnesium become more basic than their sp^2- or sp-bonded counterparts. In other words, alkyl Grignard reagents are stronger bases than aryl, benzyl, vinyl, or acetylenic Grignard when complexed with HMPA.[10]

In order to evaluate the scope of aryl Grignard coupling, *p*-biphenylmagnesium bromide was added as its HMPA complex in THF to an ethereal solution of the chloromethyloxazine. The coupled adduct was then hydrolyzed, without purification, to *p*-biphenylacetic acid (**15**)

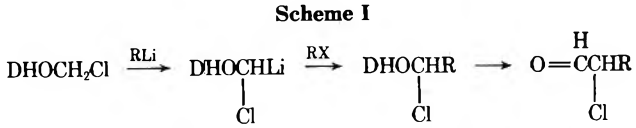


14 **15**

in 48% overall yield. Similarly, phenylmagnesium bromide was transformed into phenylacetic acid in 57% overall yield. It, therefore, seems reasonable to conclude that aryl Grignard reagents may be homologated to their acetic acid derivative by simple coupling with the chloromethyloxazine. Two-carbon homologation of vinyl, benzyl, and acetylenic Grignard reagents should likewise take place, although these experiments have not been performed.

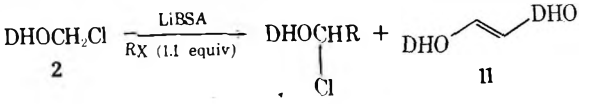
Reaction of Chloromethyloxazine 2 with Organolithium Reagents. In view of the fact that the HMPA-complexed Grignard reagents removed the α proton of the chloromethyloxazine leading to the bis(oxazinyl)ethylene **11**, it was desirable to evaluate the more basic organolithium reagents which might lead to a stable oxazine carbanion. If this could be realized, then a route to α-chloro aldehydes and α-chloro aicds would be cleared (Scheme I).

Scheme I



Treating **2** with *n*-butyllithium in THF or ether, at −78°, followed by addition of ethyl iodide, produced a mixture of products, the major one being the desired 2-(α-chloropropyl)oxazine **16**. Also found were the ethyleneoxazine **11** and varying amounts of dialkylated chlorooxazine **17**. Varying the quantities of *n*-butyllithium from 1.0 to 2.0 equiv effected only slight changes in the composition of the mixture. When 1.0 equiv of *n*-butyllithium was employed, little or no dialkylated product **17** was formed. In contrast to these results, the use of *tert*-butyllithium followed by introduction of methyl iodide gave generally lower yields of the desired alkylated prod-

Table II
Alkylation of 2-Chloromethyloxazine with Lithium Bis(trimethylsilyl)amide (LiBSA) in Tetrahydrofuran

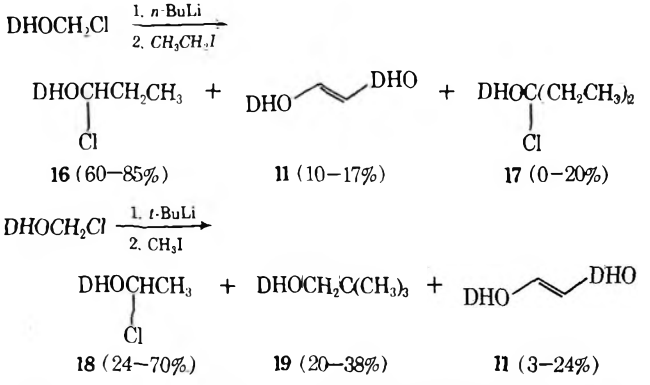


18, R = CH_3
16, R = C_2H_5

Entry	Equiv	RX	Temp,[a] °C	Time, hr[b]	% 2	% 16 or 18	% 11[f]
1	1	CH_3I	−78	0.5	40	60	0
2	2	CH_3I	−78	0.5	3	97	0
3	2	CH_3I	−78	2.0	2	97	1
4	2	CH_3I	−30	2.0	2	68	30
5	2	CH_3I	0	1.0	2	36	62
6	2	CH_3I	−78	*c*	2	98	0
7	2	CH_3CH_2I	−78	0.5	0	100[d]	0
8	2	CH_3CH_2Br	−78	0.5	1	93[e]	6
9	2	CH_3CH_2Cl	−78	0.5	16	7	77

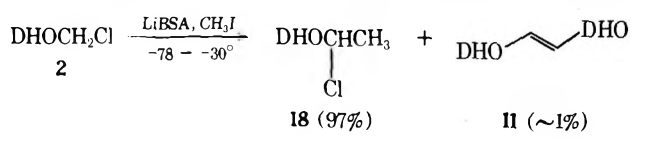
[a] Temperatures at which **2** and base were mixed. [b] Time elapsed prior to addition of alkyl halide at the temperatures indicated. Reaction solutions were allowed to gradually warm to room temperature. [c] Methyl iodide added to solution of base followed by addition of **2**. [d] Contained 7% dialkylated material, **17**. [e] Contained 3% dialkylated material, **17**. [f] Product ratios were determined by vpc; isolated yields of **16** or **18** were slightly lower.

uct **18** along with the coupling product **19**. The disappointing results obtained with alkyllithium reagents, namely coupling, polyalkylation, and reactions between **2** *and its lithio salt, rendered the feasibility of Scheme I* questionable.



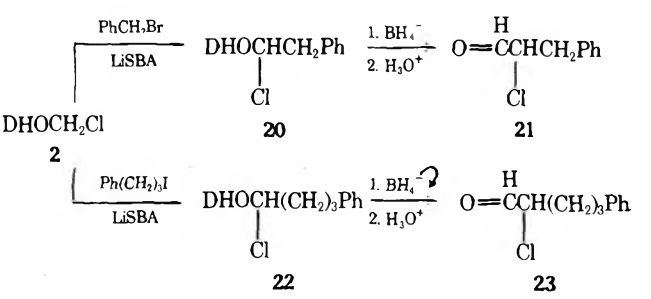
Attention was then focused on an alternative base, lithium bis(trimethylsilyl)amide (LiBSA), as a suitable reagent which might minimize both coupling and polyalkylation owing to its steric bulk and poor nucleophilic character. This base has been successfully used by Rathke[11] in his elegant alkylation of acetic esters. Furthermore, the base is conveniently prepared from hexamethyldisilazane[12] and is a stable, easily handled reagent soluble in both polar and nonpolar solvents.

Addition of **2** to a solution of LiBSA at −78° in THF, *followed by introduction of D_2O–DCl at this temperature*, gave the chloromethyloxazine devoid of any deuterium incorporation. It thus became evident that a proton is not abstracted from **2** at this temperature. This implied that it should be possible to introduce **2**, the lithium base, and the alkyl halide all together at −78° and allow the reaction to warm slowly. When the proton is removed at some elevated temperature, the presence of the alkyl halide should allow alkylation in a style more competitive than that observed with *n*-butyl- and *tert*-butyllithium. This, indeed, proved to be the case. Allowing a THF solution containing **2**, methyl iodide (1.1 equiv), and LiBSA (2.0 equiv) to warm from −78 to −30° and then quenching gave **18** in 97% yield along with a trace of the ethylene **11**. A study was carried out to assess the stoichiometry, temperature, and nature of the halide. The results are presented in Table II.

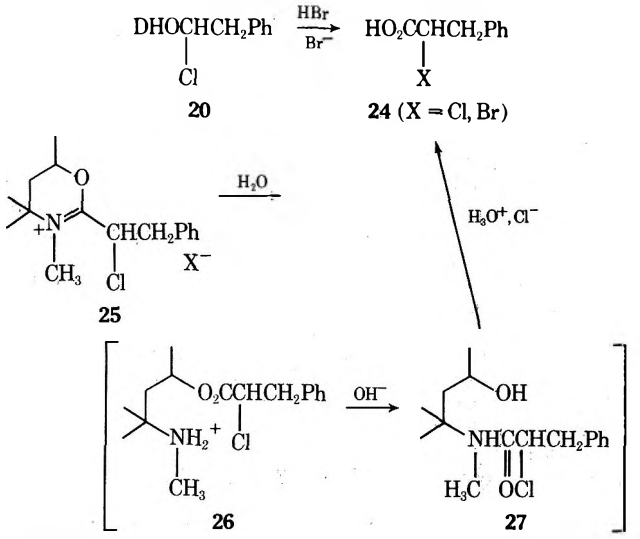


As seen from the tabulated results, 2.0 equiv of LiBSA was required to effect efficient alkylation (entry 1 and 2). Presumably, the base and chloromethyloxazine anion are in equilibrium and the excess base produced a higher concentration of the oxazine anion. The amount of ethylene product **11** becomes significant at temperatures above −30° (entries 3–5), which means that the anion is forming very rapidly at these temperatures and coupling with **2** is facile. It is also evident from Table II that the order of introduction of the reactants at −78° is of no consequence (entry 2 and 6), since, as already mentioned, no reaction takes place at this temperature. Varying the halogen from Cl to Br to I gave the expected results (entries 7–9). Reaction with ethyl chloride was poor as seen by the 7% yield of alkylated product. The anion undoubtedly preferred reaction with the chloromethyloxazine, producing the ethylene product in 77% yield. The small quantity of diethylated material in entries 7 and 8 was readily removed by distillation and presented no difficulties in preparative runs.

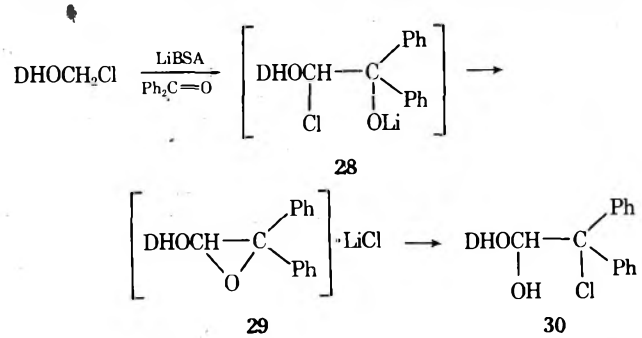
In order to demonstrate that this technique was indeed useful for the preparation of α-chloro aldehydes, **2** was alkylated with benzyl bromide and 3-phenylpropyl iodide, giving the elaborated oxazines **20** and **22**, respectively. Subjecting these oxazines to the usual borohydride reduction[13] and acidic hydrolysis furnished the α-chloro aldehydes **21** and **23** in overall yields (from **2**) of 55 and 53%, respectively. This synthesis of α-chloro aldehydes, therefore, provides a useful alternative to the existing methods which involve direct chlorination.[14] The addition of dichloromethyllithium to carbonyl compounds[15] is also noteworthy.



Since oxazines have been hydrolyzed to carboxylic acids, this sequence should be applicable to α-chlorocarboxylic acids. Heating **20**, for example, with aqueous hydrobromic acid–sodium bromide did produce the carboxylic acid **24** in good yield, but as a mixture of the chloro and bromo derivatives. The poor results obtained on hydrolysis using hydrochloric acid[16] precluded its use. A milder, more efficient oxazine cleavage was achieved by converting **20** to its methosulfate salt **25** (X = $OSO_3CH_3^-$) and treating it with water. This gave the open-chain amino ester **26** in good yield. The latter was stirred in a weakly alkaline solution for a few minutes, which afforded the amide **27**. Reacidification with 9 *N* hydrochloric acid resulted in amide cleavage and furnished the α-chloro acid **24** (X = Cl) in 82% yield. The entire cleavage operation was carried out in a single vessel without isolation of any of the intermediates.[17] The methiodide salt **25** (X = I) could not be employed in this sequence owing to its instability. Upon standing, the iodide ion in **25** reacts with the chlorine substituent, generating copious amounts of iodine vapor.



In an effort to vary the nature of the electrophile that could react with the chloromethyloxazine carbanion, it is unfortunate that enolizable carbonyl compounds must be excluded. This is due to the fact that current conditions require all the reactants to be present simultaneously at −78°. For nonenolizable carbonyl compounds, reactions with LiBSA have also been reported.[18] Nevertheless, when a solution of **2**, benzophenone, and 2.0 equiv of LiBSA was allowed to warm slowly from −78 to 0° and quenched, the chlorohydrin **30** was obtained in 65% yield. Of interest is the fact that the hydroxy group in **30** is α to the oxazine ring, which probably arose from the initial adduct **28** passing through the epoxide **29**. The latter rearranged either under the influence of lithium chloride[19] or during the aqueous work-up which involved dilute hydrochloric acid.



In summary, the 2-chloromethyloxazine appears to possess the potential for elaborating aryl Grignard reagents by two carbons to their acetic acid derivatives and further provides a route to α-chloro aldehydes and carboxylic acids. In the accompanying paper, the chloromethyloxazine is shown to serve as a useful precursor to phosphorus ylides and carbanions whose synthetic utility will be demonstrated.

Experimental Section

Melting points and boiling points are uncorrected. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn., Midwest Microlabs, Inc., Indianapolis, Ind., and Atlantic Microlabs, Inc., Atlanta, Ga. Infrared spectra were determined on a Perkin-Elmer 257 grating spectrophotometer. The nmr spectra were measured with Varian A-60A and T-60 instruments using carbon tetrachloride or deuteriochloroform as solvent containing tetramethylsilane (~1%) as the internal standard. Mass spectra were obtained on an Atlas CH-4 spectrometer at 70 eV. Thin layer chromatography (tlc) was carried out on silica gel G (PF_{254}). The chromatograms were developed in an iodine chamber. Preparative thick layer chromatography (plc) was performed on silica gel G (PF_{254}) and visualization of the chromatogram was effected by exposure to short-wave uv light (Blak-Ray UVL-21). Vapor phase chromatography (vpc) analyses were performed on an F & M Model 810 (thermal conductivity) chromatograph with column A, 10 ft × 0.25 in. o.d. copper tubing containing 7% (w/w) Silicone Fluid SE-30 on Chromosorb P; a Hewlett-Packard Model 5750 (flame ionization) chromatograph with column B, 6 ft × 0.125 in. o.d. stainless steel UCW 98, 80–100 mesh, column C, 18 ft × 0.125 in. o.d. UCW 98; or a Hewlett-Packard Model 5750 (thermal conductivity) chromatograph with column D, 6 ft × 0.25 in. o.d. copper tubing containing 10% (w/w) Silicone Fluid SE-31 on Diatoport S. Hexamethylphosphoric triamide (HMPA) was dried over molecular sieves (Linde) and distilled onto molecular sieves for storage under argon.

2-Chloromethyl-4,4,6-trimethyl-5,6-dihydro-1,3-oxazine (2). To a 500-ml flask equipped with a thermometer, a stirrer, and a 125-ml addition funnel was added 100 ml of concentrated sulfuric acid. The acid was cooled to 0–5° with an ice–acetone bath and 41.6 g (0.55 mol) of chloroacetonitrile was added at such a rate that the temperature was maintained at 0–5°. After the addition of the nitrile was completed, 59 g (0.4 mol) of 2-methyl-2,4-pentanediol was added at such a rate that the same temperature (0–5°) was maintained. The mixture was stirred for an additional 1 hr and then poured onto 400 g of crushed ice. The aqueous solution was extracted with four 50-ml portions of methylene chloride (and the methylene chloride extracts were discarded). The cold aqueous acid solution was carefully poured into a cooled (0°) beaker containing 400 g of sodium bicarbonate and 300 ml of diethyl ether. Upon becoming neutral a red-yellow oil appeared that was taken up in the ether layer. The aqueous layer was extracted with four 200-ml portions of diethyl ether (water was added as needed) and the combined ether extracts were dried over anhydrous potassium carbonate. The ether was removed by rotary evaporation and the residue was distilled through a 20-cm fractioning column to give 47–57 g (55–63%) of a colorless liquid: bp 41° (1.0 mm); ir (film) 1665 cm^{-1}; nmr (CCl_4) δ 1.2 (s, 6), 1.3 (d, 3), 1.7 (d of t, 2), 3.9 (s, 2), 4.2 (m, 1).

The product can be stored indefinitely under nitrogen at −20° over a few grains of potassium carbonate.

Anal. Calcd for $C_8H_{14}NOCl$: C, 54.70; H, 8.03; N, 7.97. Found: C, 54.92; H, 7.98; N, 7.76.

Treatment of 2-Chloromethyl-4,4,6-trimethyl-5,6-dihydro-1,3-oxazine (2) with Various Grignard Reagents in Ether or in THF. In general, coupling reactions attempted between **2** and excess Grignard reagents gave mixtures as described in the discussion. The mixtures were analyzed on vpc volumns B and D and by tlc and nmr. Assignments of structure were made by comparison of isolated materials with authentic samples prepared by alternate routes.[3] The following procedure is a typical one.

Treatment of 2 with 2 Equiv of Phenylmagnesium Bromide in Ethyl Ether. Phenylmagnesium bromide was prepared in the usual way from magnesium (3.14 g, 0.02 mol) in ether (30 ml). It was then added slowly to **2** (1.76 g, 0.01 mol) in ether (20 ml) and heated to reflux for 16 hr. The dark mixture was then cooled in an ice bath, 5 ml of cold 1 *N* hydrochloric acid was added slowly, and the mixture was poured over ice and made acidic (pH ~3). The acidic mixture was extracted with ether (3 × 50 ml) and the

ether extracts were discarded. The aqueous solution was neutralized with sodium bicarbonate and the neutral mixture was extracted with ether (4 × 50 ml). The neutral ether extracts were dried over potassium carbonate and evaporated to give 1.49 g of brown liquid. The nmr and ir spectra were consistent with a 70:30 mixture of 2-phenyl-1,3-oxazine **9** and 2-benzyl-1,3-oxazine **10**.[3] The products did not separate on vpc columns B, C, or D. The mixture was separated by elution on a silica gel (28–200 mesh) column with ether. The oxazine **9** was the first component to elute from the column, followed by **10**.

Treatment of 2 with 1 Equiv of Phenylmagnesium Bromide in the Presence of 2 Equiv of HMPA. Preparation of 10 from 2. Phenylmagnesium bromide was prepared from magnesium (0.3 g) and bromobenzene (1.57 g, 0.01 mol) in THF (20 ml). To the Grignard solution was added HMPA (3.58 g, 0.02 mol), which became warm on mixing. The solution was added slowly to **2** (1.76 g, 0.01 mol) in ether (35 ml) *via* syringe and the resultant solution was refluxed for 18 hr. The solution was poured into ice water, made acidic (pH ~3), and extracted with ether, and the ether extracts were discarded. The aqueous acid solution was neutralized with sodium bicarbonate and extracted with ether, and the neutral ether extracts were dried and evaporated to yield an amber product (1.66 g) which consisted of **10**[3] (85%) and recovered **2** (15%).

Reaction of 2 with 1 Equiv of Phenylmagnesium Bromide in 50:50 HMPA–THF. Preparation of 11. Phenylmagnesium bromide was prepared as described above. To the Grignard solution was added HMPA (3.58 g, 0.02 mol). On mixing, some heat was liberated. The resultant solution was then added slowly to **2** (1.76 g, 0.01 mol) in a mixture of THF (25 ml) and HMPA (25 ml) and heated to reflux for 18 hr. The product was isolated as in the previous reaction. The crude product (1.20 g) was recrystallized from cold ethyl ether, giving 1.12 g (80%) of **11**: white needles, mp 161°; ir 1631 cm^{-1}; nmr (CCl_4) δ 6.4 (s, 2), 4.1 (m, 2), 1.32 (d, 6), 1.2 (s, 12); mass spectrum *m/e* (rel intensity) 278 (20), 180 (100).

Anal. Calcd for $C_{16}H_{26}N_2O_2$: C, 69.03; H, 9.41; N, 10.06. Found: C, 68.97; H, 9.52; N, 10.13.

***p*-Biphenylacetic Acid (15).** *p*-Biphenylmagnesium bromide was prepared from magnesium (0.6 g) and *p*-bromobiphenyl (5.12 g, 0.022 mol) in THF (50 ml). To the biphenylmagnesium bromide solution was added HMPA (8 ml). The resultant solution was added slowly to a solution of **2** (3.5 g, 0.02 mol) in ethyl ether (100 ml). The mixture was refluxed for 18 hr and the product, a thick yellow liquid, was isolated as in the previous experiment. The nmr spectrum of the crude material showed a mixture of starting material **2**, the desired oxazine adduct **14**, and traces of HMPA. The crude product was then added to a hydrobromic acid solution (0.08 mol of HBr in 30 ml of H_2O saturated with NaBr); this refluxed for 18 hr. The acidic mixture was extracted with chloroform and the organic layer was washed with brine. Benzene (10 ml) was added to the chloroform solution and the solution was evaporated to give a tan solid (2 g, 47%), which was recrystallized from ethyl ether to give pure *p*-biphenylacetic acid **15** (1.7 g, 41%), white needles, mp 165° (lit.[20] mp 164°).

Reaction of 2 with *tert*-Butyllithium. To 40 ml of THF at −78° under nitrogen was added *tert*-butyllithium (0.011 mol in pentane) followed by **2** (1.76 g, 0.01 mol) in 10 ml of THF. The mixture was stirred for 30 min and methyl iodide (1.41 g, 0.01 mol) was then added *via* syringe. The mixture was allowed to stir for 2 hr, poured into cold 1 *N* hydrochloric acid (~25 ml), and extracted with pentane, and the pentane extracts were discarded. The aqueous acid solution was neutralized with sodium bicarbonate, extracted with ether, and concentrated to yield a yellow liquid (1.4 g), which was analyzed by vpc on column B (100–250°). The material recovered was found to be a mixture with the following composition: **18** (24%), **19** (38%), **11** (24%), and recovered **2** (3%). Products were identified by comparison of their physical properties to those of authentic samples. Oxazine **19**, which had not been previously prepared, was isolated by preparative layer chromatography using ether–pentane (3:1) as the eluent, R_f 0.75. Another sample was collected from the vpc instrument, column C, 135°: ir (film) 1665 cm^{-1}; nmr (CCl_4) δ 4.1 (m, 1), 2.0 (s, 2), 1.5 (m, 2), 1.3 (d, 3), 1.1 (s, 6), 1.0 (s, 9).

Anal. Calcd for $C_{12}H_{23}NO$: C, 73.04; H, 11.75; N, 7.10. Found: C, 72.84; H, 11.66; N, 7.24.

Lithium Bis(trimethylsilyl)amide (LiBSA). The procedure of Amonoo-Neizer[12] was followed. *n*-Butyllithium (0.3 mol) in hexane (2.56 *M*) was added slowly to a stirred solution of freshly distilled hexamethyldisilazane (51.5 g, 0.32 mol) in ether (100 ml). The mixture was heated to reflux, the solvents were evaporated, and the residue was dried under vacuum. The residue was then dissolved in THF to obtain a 2 *M* solution and used in the subsequent reactions.

2-(1-Chloroethyl)-4,4,6-trimethyl-5,6-dihydro-1,3-oxazine (18). A 50-ml portion of a 2 *M* solution of LiBSA, prepared as above and cooled to −78° in Dry Ice–acetone under nitrogen, was treated with 8.8 g (0.05 mol) of **2** in 10 ml of THF. MeI (8.46 g, 0.06 mol) in 10 ml of THF was slowly added *via* syringe. The resultant solution was allowed to slowly warm to 0° (3–3.5 hr) and poured into cold 6 *N* hydrochloric acid solution (40 ml). The acid solution was extracted with petroleum ether and the extracts were discarded. The acid solution was then neutralized using sodium bicarbonate and extracted with ether. The ether extracts were evaporated and the residue was distilled, furnishing 8.14 g (85%) of **18**: bp 44° (1.3 mm); ir (film) 1665 cm^{-1}; nmr (CCl_4) δ 4.3 (q, 1), 4.2 (m, 1), 1.7 (d of t, 2), 1.6 (d, 3), 1.3 (d, 3), 1.1 (s, 6). Vpc analysis on column C (135°) indicated that the material contained less than 1% of **2**.

Anal. Calcd for $C_9H_{16}NOCl$: C, 56.99; H, 8.50; N, 7.33. Found: C, 57.04; H, 8.43; N, 7.08.

2-(1-Chloropropyl)-4,4,6-trimethyl-5,6-dihydro-1,3-oxazine (16) was prepared in the same manner as **18**, using ethyl iodide. Oxazine **16** was obtained in 92% yield (distilled), bp 45° (0.4 mm); vpc analysis on column B (135°) indicated the absence of **2** and less than 1% dialkylated material (**17**); ir (film) 1665 cm^{-1}; nmr (CCl_4) δ 4.2 (m, 1), 4.0 (t, 1), 1.9 (m, 2), 1.7 (m, 2), 1.3 (d, 3), 1.1 (s, 6), 0.9 (t, 3); mass spectrum *m/e* (rel intensity) 205 (6), 203 (16), 168 (48), 84 (100).

2-(1-Chloro-2-phenylethyl)-4,4,6-trimethyl-5,6-dihydro-1,3-oxazine (20). Using the above procedure, **2** was treated with benzyl bromide or benzyl chloride and the reaction was quenched at −30°. A 72 and 68% yield, respectively, of **20** was obtained: bp 98° (0.15 mm); solidified mp 65–66.5° (pentane); ir (film) 3080–3020, 1665, 1605 cm^{-1}; nmr (CCl_4) δ 7.2 (s, 5), 4.3 (t, 1), 4.1 (m, 1), 3.2 (d of d, 2), 1.5 (d of t, 2), 1.3 (d of d, J = 1 Hz, 3), 1.1 (d, J = 1 Hz, 3), 0.9 (s, 3).

Anal. Calcd for $C_{15}H_{20}NOCl$: C, 67.80; H, 7.60; N, 5.26. Found: C, 67.54; H, 7.77; N, 5.32.

2-Chloro-3-phenylpropanal (21). The oxazine **20** was reduced with sodium borohydride according to the general procedure previously described.[3] The excess sodium borohydride was destroyed at −45° with 3 *N* hydrochloric acid solution to avoid halogen removal. The crude isolated aldehyde, after oxalic acid hydrolysis, gave a single peak on vpc analysis (column B, 155°). Distillation afforded pure material: bp 112° (13 mm); $n^{25}D$ 1.5358 (lit.[21] $n^{14}D$ 1.5375); ir (film) 1735 cm^{-1}; nmr (CCl_4) δ 9.63 (J = 2 Hz, d, 1); semicarbazone mp 199°.

2-(1-Chloro-4-phenylbutyl)-4,4,6-trimethyl-5,6-dihydro-1,3-oxazine (22). Using the above procedure, **2** was treated with 1-iodo-3-phenylpropane and the reaction was quenched at 0°. Oxazine **22** was obtained in 83% yield: bp 115° (0.05 mm); ir 3080–3020, 1665, 1605 cm^{-1}; nmr (CCl_4) δ 7.2 (s, 5), 4.2 (m, t, 2), 2.6 (t, 2), 1.4–2.2 (m, 4), 1.3 (d, 3), 1.2 (s, 6); mass spectrum *m/e* (rel intensity) 293 (5), 295 (16), 258 (27), 175 (100), 141 (27).

2-Chloro-5-phenylpentanal (23). Oxazine **22** was reduced with sodium borohydride and the aldehyde **23** was released[3] after oxalic acid hydrolysis. Distillation furnished pure α-chloro aldehyde: bp 77° (0.075 mm); ir (film) 1730 cm^{-1}; nmr (CCl_4) δ 9.4 (d, J = 2 Hz, 1), 7.2 (m, 5), 4.1 (m, 1), 2.7 (t, 2), 1.4–2.2 (m, 4); semicarbazone mp 204°.

Anal. Calcd for $C_{11}H_{13}ClO$: C, 67.11; H, 6.65. Found: C, 67.39; H, 6.73.

2-Chloro-3-phenylpropionic Acid (24). To 25 ml of ether, under nitrogen, was added dimethyl sulfate (2.52 g, 0.02 mol) and **20** (2.66 g, 0.01 mol). The solution was stirred overnight, during which time an oil separated from solution. The ether was evaporated, cold water was added, and the resulting acidic solution was made basic (pH ~10 for 5 min). The mixture was again made acidic by addition of 9 *N* hydrochloric acid (pH ~1) and the solution was heated to reflux overnight. The mixture was extracted with chloroform, and the chloroform extracts were dried (sodium sulfate) and evaporated. The residue was distilled, giving 1.52 g (82%) of **24**: bp 170° (2 mm) [lit.[22] bp 170–174° (25 mm)]; ir 3500–2400, 1745, 1605 cm^{-1}; nmr ($CDCl_3$) δ 11.9 (b, 1), 7.15 (s, 5), 4.4 (t, 1), 3.3 (d of t, 2).

2-(2-Chloro-1-hydroxy-2,2-diphenylethyl)-4,4,6-trimethyl-5,6-dihydro-1,3-oxazine (30). Using the above procedure, **2** was treated with benzophenone and the reaction was quenched at 0°. Oxazine **30** was obtained in 63% yield: mp 130° (hexane); ir (KBr) 3110, 1665 cm^{-1}; nmr (CCl_4) δ 7.0–7.8 (m, 10), 6.8 (s, 1, exchangeable with D_2O), 5.0 (s, 1), 4.0 (m, 1), 0.6–1.7 (m, 1); mass spectrum *m/e* (rel intensity) 322, 182, 140, 105 (100).

Anal. Calcd for $C_{21}H_{24}NO_2Cl$: C, 70.48; H, 6.76; N, 3.91. Found: C, 70.62; H, 6.84; N, 3.71.

Acknowledgment. The authors are grateful to the National Science Foundation (GP22541), the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the National Institutes of Health for financial support of this work. Generous supplies of organolithium reagents from the Lithium Corporation of America are also gratefully acknowledged.

Registry No.—**2**, 50259-03-5; **11**, 50259-04-6; **15**, 5728-52-9; **16**, 50259-06-8; **18**, 50259-07-9; **19**, 50259-08-0; **20**, 50259-09-1; **21**, 19261-37-1; **22**, 50259-11-5; **23**, 50546-23-1; **24**, 20334-70-7; **30**, 50259-13-7; HMPA, 680-31-9.

References and Notes

(1) Part XXII of a study on the chemistry of 5,6-dihydro-1,3-oxazines. For previous papers in this series, see A. I. Meyers, A. C. Kovelesky, and A. J. Jurjevich, *J. Org. Chem.*, **38**, 2136 (1973).
(2) Address all correspondence to this author at the Department of Chemistry, Colorado State University, Fort Collins, Colo. 80521.
(3) A. I. Meyers, A. Nabeya, H. W. Adickes, I. R. Politzer, G. R. Malone, A. C. Kovelesky, R. L. Nolen, and R. C. Portnoy, *J. Org. Chem.*, **38**, 36 (1973).
(4) A. I. Meyers, E. M. Smith, and M. S. Ao, *J. Org. Chem.*, **38**, 2129 (1973).
(5) M. S. Kharasch and O. Reinmuth, "Grignard Reactions of Non-Metallic Substances," Prentice-Hall, Englewood Cliffs, N. J., 1954, p 1060.
(6) E. J. Tillmanns and J. J. Ritter, *J. Org. Chem.*, **22**, 839 (1957).
(7) H. Normant, *Angew, Chem., Int. Ed. Engl.*, **6**, 1046 (1967).
(8) G. Stork, P. A. Grieco, and M. Gregson, *Tetrahedron Lett.*, 2181 (1969).
(9) A. I. Meyers and E. W. Collington, *J. Amer. Chem. Soc.*, **92**, 6676 (1970).
(10) In a collateral experiment, **2** was treated with cyclopropylmagnesium bromide·2HMPA and gave a 35% yield of the 2-cyclopropylmethyloxazine (**1**, R = CH_2-c-C_3H_5), 48% recovered starting material, and only 17% of the bis(oxazinyl)ethylene **11**. This is consistent with the increased s character of the cyclopropyl carbanion whose base strength should lie somewhere between those of an aliphatic and an aromatic Grignard reagent.
(11) M. W. Rathke, *J. Amer. Chem. Soc.*, **92**, 3222 (1970).
(12) E. H. Amonoo-Neizer, R. A. Shaw, D. O. Skovlin, and B. C. Smith, *J. Chem. Soc.*, 2997 (1965).
(13) C. L. Stevens and B. T. Gillis, *J. Amer. Chem. Soc.*, **79**, 3449 (1957).
(14) A. Lorenzini and C. Walling, *J. Org. Chem.*, **32**, 4008 (1967).
(15) G. Kobrich and W. Werner, *Tetrahedron Lett.*, 2181 (1969).
(16) A. I. Meyers, I. R. Politzer, B. K. Bandlish, and G. R. Malone, *J. Amer. Chem. Soc.*, **91**, 5886 (1969).
(17) A number of *N*-methyloxazinium salts (*e.g.*, **25**) have been shown in these laboratories to rapidly open to the amino esters (*e.g.*, **26**) upon addition of water and rearrange smoothly to the hydroxy amides when dilute alkali is introduced; *cf.* Z. Eckstein and T. Urbanski, *Advan. Heterocycl. Chem.*, **2**, 336 (1963).
(18) C. Kruger, E. C. Rochow, and U. Wannagat, *Ber.*, **96**, 2131 (1963).
(19) B. C. Hartman and B. Rickborn, *J. Org. Chem.*, **37**, 943 (1972).
(20) E. Schwenk and D. Papa, *J. Org. Chem.*, **11**, 798 (1946).
(21) A. Kirrmann, R. Muth, and J. Kiehl, *Bull. Soc. Chim. Fr.*, 1469 (1958).
(22) M. L. Bender and B. W. Turnquest, *J. Amer. Chem. Soc.*, **77**, 427 (1955).

The Chemistry of 2-Chloromethyloxazines. Formation of Phosphoranes and Phosphonates. The Use of α,β-Unsaturated Oxazines as a Common Intermediate for the Synthesis of Aldehydes, Ketones, and Acids[1]

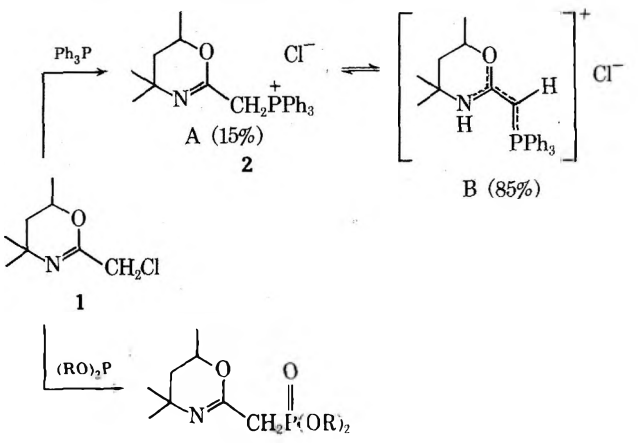
G. Ray Malone and A. I. Meyers*[2]

Department of Chemistry, Wayne State University, Detroit, Michigan 48202

Received August 31, 1973

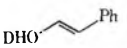
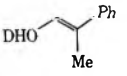
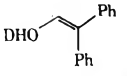
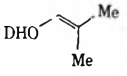
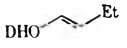
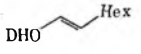
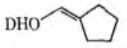
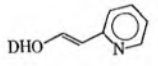
The 2-chloromethyloxazine **1** has been found to yield phosphonium salts **2** and phosphonates **3** which serve as "Wittig-type" reagents upon reaction with carbonyl compounds. The resulting α,β-unsaturated oxazines **5**, in turn, have been shown to serve as a common precursor to unsaturated aldehydes, ketones, and acids by (a) sodium borohydride reduction of **5** or their *N*-methyl quaternary salts **24**, (b) addition of organolithium reagents to the *N*-methyl quaternary salts **24**, and (c) hydrolysis of **24** in aqueous medium.

The availability of the 2-chloromethyloxazine **1** and its successful use of an electrophile[1] has prompted an investigation into its potential role as a precursor to oxazine "Wittig-type" reagents. Reaction of **1** with triphenylphosphine provided a 75% yield of the phosphonium salt **2** as a 1:5.7 mixture of tautomers A and B. The infrared spectrum of **2** (chloroform) showed only weak absorption at 1660–1670 cm^{-1} for the C=N link in A and strong absorption at 1603 cm^{-1}, whereas the ultraviolet spectrum (ethanol) exhibited bands at 273, 267, and 263 nm resulting from extended delocalization in B. The nmr spectrum of **2** showed a doublet at δ 4.22 (J = 15 Hz, 0.85 H) and a broad signal at δ 10.2 (0.85 H) attributable to the vinyl and NH protons, respectively, in the B tautomer. A small, broad signal at δ 2.48 was present due to the α-methylene protons in tautomer A. The highly delocalized structure in B was further confirmed by a single-crystal X-ray analysis.[3] The chloromethyloxazine also underwent a smooth Michaelis–Arbuzov reaction with trialkyl phosphites, furnishing the oxazine phosphonates **3a** (40%) and **3b** (80%). Both **2** and **3b** were allowed to react with a variety of carbonyl compounds in order to assess their ability to form olefinic derivatives.



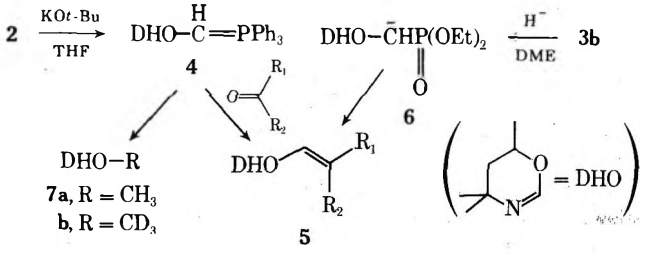
When a suspension of **2** in THF was treated with potassium *tert*-butoxide, a yellow solution of the phosphorane **4** formed immediately. The phosphorane reacted rapidly and exothermally with aldehydes, giving good yields of the *trans*-vinyl oxazines **5** (R_2 = H). Reactions with ketones were more sluggish, requiring overnight heating and resulting, where possible, in mixtures of geometric isomers

Table I
Coupling of Oxazines 2 and 3b with Carbonyl Compounds

R_1	R_2	Vinyl oxazine 5	Yield, % From 2	Yield, % From 3b	Bp, °C (mm)	λ (EtOH), nm (ε)	ν, cm⁻¹ (film)
Ph	H		94	80	110 (0.4)	274 (27,000)	1613 (s) 1644 (s)
Ph	Me		70[a]	57[b]	122 (1.5)	275 (22,000)	1611 (m) 1645 (s)
Ph	Ph		52	77	80[c]	275 (20,000)	1603 (s) 1636 (s)
Me	Me		50	73	55 (1.5)	222 (14,000)	1612 (s) 1645 (s) 1655 (s)
Et	H		80	75	56 (1.0)	212 (19,600)	1626 (s) 1653 (m) 1663 (s)
n-Hex	H		82	72	110 (1.3)	213 (16,000)	1620 (s) 1647 (m) 1664 (s)
$-(CH_2)_4-$			48	77	80 (0.5)		1608 (s) 1634 (s) 1658 (s)
2-C_5H_4N	H		72	65	128 (0.5)		1599 (m) 1613 (s) 1653 (s)

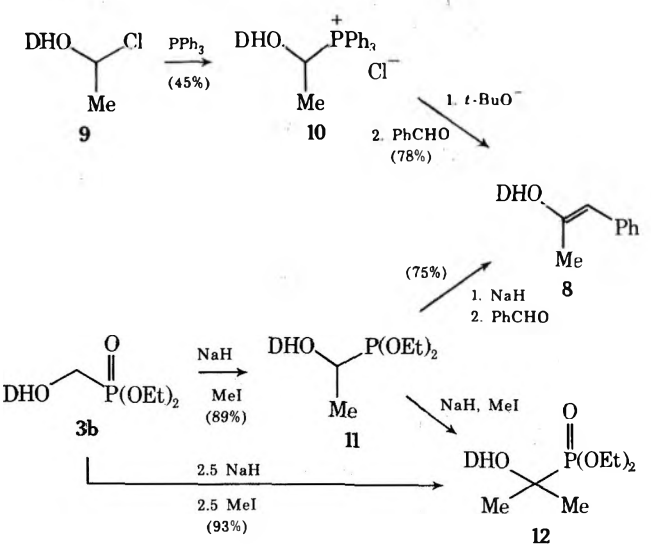
[a] 50:50 cis–trans mixture. [b] 24:76 cis–trans mixture. [c] Melting point.

(Table I). Furthermore, simple alkaline hydrolysis of the phosphorane 4 readily gave the 2-methyldihydroxazine **7a**.[4] When the hydrolysis was performed in D_2O–NaOD, a 70% yield of the 2-trideuteriomethyloxazine **7b** was isolated. This method, in which the deuterated oxazine can be obtained in quantity, should provide a route to tetradeuterioacetaldehyde[4] and other α-deuterioacetaldehyde derivatives. Treatment of the oxazine phosphonate **3b** with sodium hydride in dimethoxyethane cleanly produced the anion **6**. Its reaction with carbonyl compounds was found to be more efficient and occurred smoothly at room temperature, (Table I). The reaction of **6** with acetophenone gave a 24:76 mixture of **5**. The isomer containing the phe-

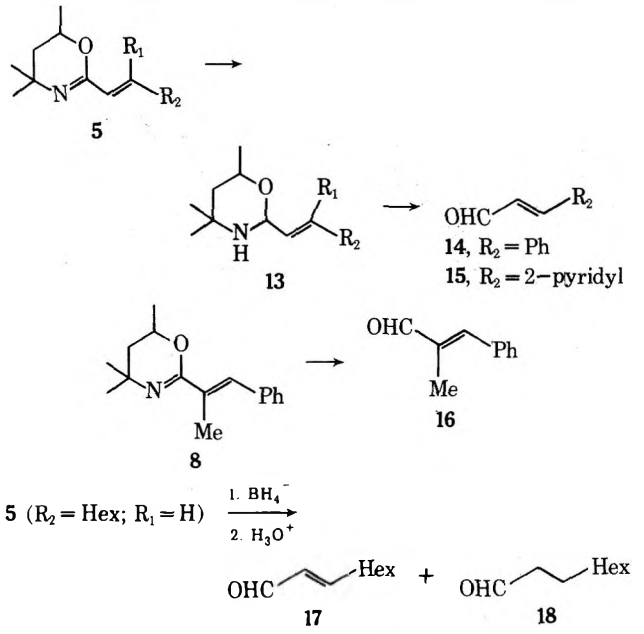


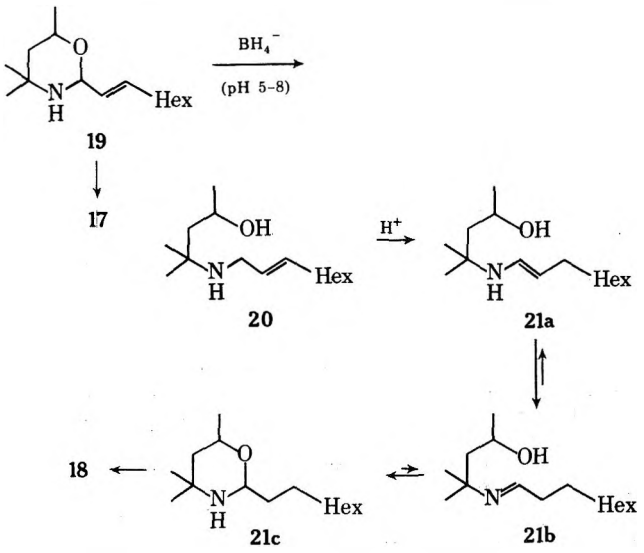
nyl group trans to the oxazine ring was the predominant product. The isomer ratio from acetophenone and **4** was approximately 50:50. On heating to 180° for 45 min, the mixture was brought to thermal equilibrium, furnishing a 15:85 cis–trans mixture. Thus, the oxazine phosphonate anion **6**, at room temperature, couples with ketones to give nearly thermodynamic products.

It was desired to extend the preparation of vinyl oxazines to the α-methyl derivative **8**. As stated previously,[1] the value of the oxazines in synthesis depends greatly on the degree to which the 2 substituent can be varied. Introduction of the α-methyl group (*i.e.*, **8**) would lead to α-methyl aldehydes, ketones, or acids. The preparation of **8**, as a suitable example to accomplish these goals, was successfully achieved *via* two routes. Conversion of the 2-(α-chloroethyl)oxazine **9**[1] to its phosphonium salt **10** took place upon heating with triphenylphosphine in xylene. The yield of **10** was 45% and examination of its spectral properties revealed that it represented a highly delocalized ion similar to the phosphonium salt **2**. Addition of potassium *tert*-butoxide followed by addition of benzaldehyde provided the trisubstituted olefin **8** in 78% yield. Attempts to increase the efficiency of this sequence by starting with the phosphonium salt **2** and generating **10** *in situ* led to mixtures containing **2** (35%) and **10** (65%) and ultimately to di- and trisubstituted oxazine olefins **5** (R_2 = H; R_1 = Ph) and **8**, respectively. Employing the oxazine phosphonate **3b**, the α-methyl derivative **11** was obtained by treating the anion of **3b** with 1 equiv of methyl iodide. Distillation gave the monomethyloxazine phosphonate in 89% yield and 5–8% of the dimethyloxazine phosphonate **12**. Alternatively, **12** could be prepared in 93% yield by treating **3b** with excess sodium hydride and methyl iodide. It may be concluded that the oxazine phosphonium salts **2** and **10** and phosphonates **3** and **11** are indeed useful precursors to di- and trisubstituted olefins containing the oxazine moiety.

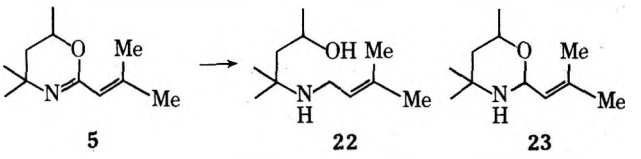


It now remained for the vinyl oxazines to demonstrate their prowess toward the preparation of carbonyl compounds. When the vinyl oxazines **5** (R = Ph, 2-pyridyl, R_1 = H) were subjected to the standard borohydride reduction,[4] the tetrahydro-1,3-oxazine **13** was produced and, without purification, hydrolyzed with aqueous oxalic acid to the α,β-unsaturated aldehydes **14** and **15**. This approach to 2-pyridylacrolein overcomes the previously reported difficulty[4] which failed to produce this compound. In a similar fashion, the oxazine **8** led to α-methylcinnamaldehyde **16** in 65% yield. On the other hand, the oxazine **5** (R = Hex), after reduction and hydrolysis, led to a 1:1 mixture of 2-nonenal (**17**) and nonanal (**18**). Examination of the nmr spectrum of the reduction product prior to hydrolysis revealed that a mixture of the expected product **19** and the overreduced product **21** was present. The latter is presumably formed by hydride attack on **19** (or the open-chain conjugated imine) in the weakly acidic medium (pH 5–8, −45°) affording the unsaturated amino alcohol **20** which rearranges to the enamine **21a**, capable of existing in tautomeric equilibrium with **21b** and **21c**.





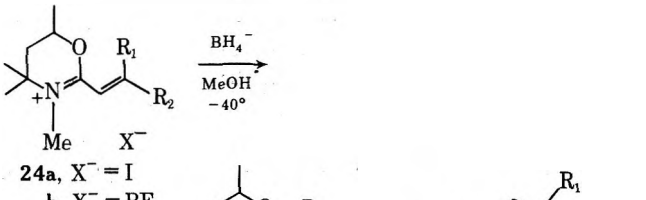
Any one of these tautomers would, on hydrolysis, lead to nonanal **18**. The possibility of sequential 1,4- and 1,2-hydride addition to **5** is also likely. However, the oxazine **5** (R_1 = R_2 = Me), when treated with sodium borohydride in weakly acidic medium (pH 5–7), gave **22** in 94% yield. This result would tend to substantiate the postulated route to nonanal (**19** → **18**) described above. The unsaturated amino alcohol **22** was found to be stable to acid solution even when heated in 3 *N* oxalic acid. Only a trace (~5%) of the desired aldehyde precursor **23** was detected

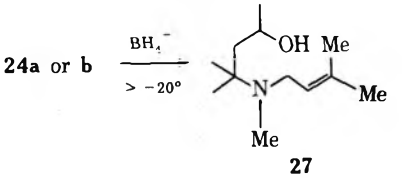


(nmr). It should also be noted that **5** (R = Hex) could be quantitatively transformed into **21** and ultimately to nonanal by performing the borohydride reduction at pH 3–5. The increased acidity in this experiment results in an enhancement of the reduction of **19** to **20**. It appears, therefore, that the conversion of vinyl oxazines **5** to α,β-unsaturated aldehydes by the standard reduction-hydrolysis technique is limited to aryl substituents on the olefin **5** (R = Ph, pyridyl, etc.). It was subsequently found that overreduction of aryl-substituted tetrahydro-1,3-oxazines **13** also occurred, albeit to a small degree (1–5%). Fortunately, rearrangement of these side products (*i.e.*, **20**, Hex = aryl) to the enamine (**21**, Hex = aryl) does not take place, as also noted for **22**, and saturated aldehydes do not contaminate the unsaturated derivatives.

In order to circumvent these undesirable side reactions, it would be necessary to by-pass both the labile tetrahydro-1,3-oxazine intermediates, **19** and **21**, and the acidic medium necessary for borohydride reduction. It is of interest to note again that the dihydrooxazines **5** and **8**, and the 2-alkyl derivatives reported earlier,[4] are virtually inert to sodium borohydride in neutral or strongly alkaline (pH >10) media.

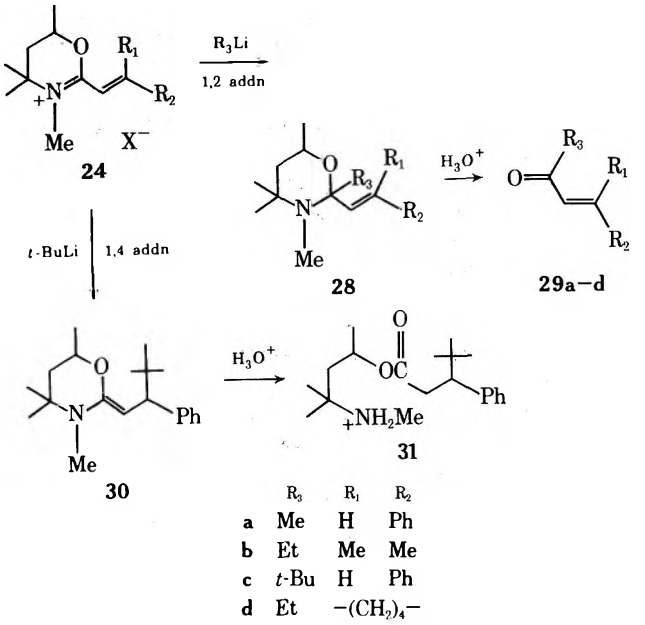
It was found that the *N*-methyl quaternary salts of the vinyl oxazines **24**, readily formed in high yield using either methyl iodide or trimethyloxonium fluoroborate, not only provided the solution to the above problem, but also served as a source of α,β-unsatrated ketones and acids. Both the iodide **24a** and the fluoroborate **24b** salts were reduced with sodium borohydride in methanol at −35 to −40° to the corresponding tetrahydro-1,3-oxazines in good yield. Acidic cleavage (oxalic acid) produced the α,β-unsaturated aldehydes **14** and **26** in 78 and 65% yields, respectively. Thus, **26**, which could not be prepared by reduction of the oxazine **5**, was readily formed *via* its *N*-methyl quaternary salt. That the reduction temperature (below −35°) was indeed critical was shown by the fact that the amino alcohol **27** was formed (~40%) when re-





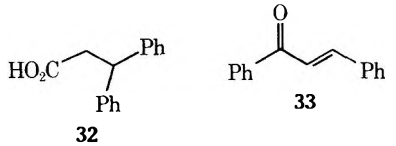
duction was performed at −20°. At 0°, the reduction of **24** gave **27** in 90% yield. Since reduction of the *N*-methyl salts gave **25** at low temperature and **25** cannot engage in ring–chain tautomerism as in the case of **21**, the route by which **27** is formed must involve direct hydride attack on the 2 position of the tetrahydro-1,3-oxazine.

As already stated, the synthetic utility of the *N*-methyl quaternary salts **24** was not limited to α,β-unsaturated aldehydes. Reaction of **24** with various organolithium reagents led to the adducts **28** which generated the α,β-unsaturated ketones **29** after hydrolysis in oxalic acid. The

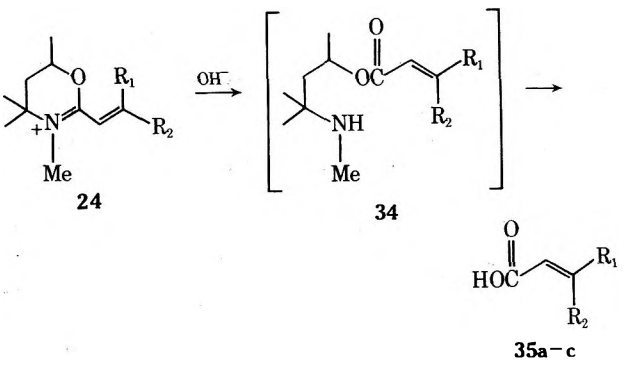


	R_3	R_1	R_2
a	Me	H	Ph
b	Et	Me	Me
c	*t*-Bu	H	Ph
d	Et	$-(CH_2)_4-$	

overall conversion, based upon the vinyl oxazines **5**, was in the range of 50–80% except for the ketone **29c** derived from *tert*-butyllithium addition. The bulky nature of this reagent resulted in addition to **24** in both a 1,2 and 1,4 fashion (**28** and **30**, respectively). The *tert*-butyl ketone was isolated after hydrolysis of **28** in 20% yield. The 1,4-addition product **30**, also present during the acidic hydrolysis, led only to the amino ester **31** and did not interfere with the isolation of the *tert*-butyl ketone. Similar behavior of ketene *N,O*-acetals related to **30** has been previously observed[5] and their ester derivatives (**31**) serve as precursors to carboxylic acids and esters by hydrolysis or transesterification. Phenylmagnesium bromide gave almost exclusive 1,4 addition to **24** (R_1 = H; R_2 = Ph), providing, after hydrolysis, an 80% yield of β,β-diphenylpropionic acid (**32**) and only a trace of chalcone **33**. It then became

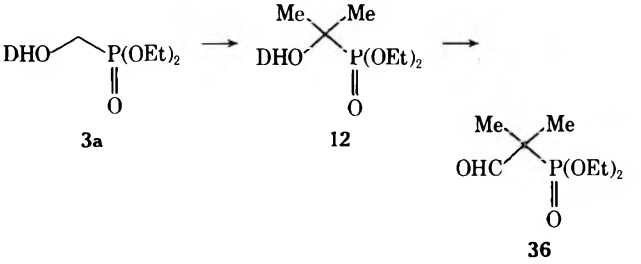


quite evident that the *N*-methyl quaternary salts also provide viable routes to carboxylic acids, simply by treatment with aqueous sodium hydroxide. Thus, **24**, on addition to dilute alkali, was found to immediately and quantitatively open to the amino ester **34**. These intermediates could be isolated and characterized and subsequently cleaved to the α,β-unsaturated acid, usually in alcoholic aqueous base. In a related study,[6] amino esters of the type **34** were shown to be readily transformed into their methyl esters by heating in methanol containing a catalytic amount of *p*-toluenesulfonic acid.



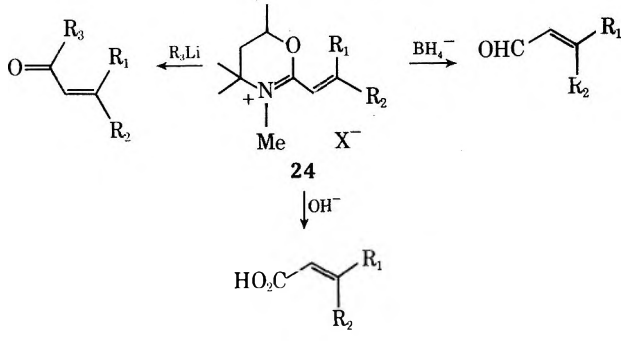
	R_1	R_2
a	Me	Me
b	Ph	H
c	$-(CH_2)_4-$	

As previously mentioned, the alkylation of **3b** with excess methyl iodide gave a high yield of the dimethyloxazine phosphonate **12**. Reduction with sodium borohydride (−40°, pH 5), after oxalic acid hydrolysis, produced the phosphonate aldehyde **36** in 62% overall yield. Thus, an entry into phosphorous-substituted aldehydes should also be feasible.



In summary, the oxazine phosphoranes and phosphonates serve as ready precursors to a variety of 2-vinyl oxazines and the latter, *via* their *N*-methyl quaternary salts (**24**), provide a common intermediate for preparing α,β-unsaturated aldehydes, ketones, and carboxylic acids (Scheme I).

Scheme I



Experimental Section

Melting points and boiling points are uncorrected. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.; Midwest Microlabs, Inc., Indianapolis, Ind.; and Atlantic Microlabs, Inc., Atlanta, Ga. Infrared spectra were determined on a Perkin-Elmer 257 grating spectrophotometer. The nmr spectra were measured with Varian A-60A and T-60 instruments using carbon tetrachloride or deuteriochloroform as solvent containing tetramethysilane (~1%) as the internal standard. Mass spectra were obtained on an Atlas CH-4 spectrometer at 70 eV.

Oxazine Phosphonium Chloride 2. A solution of 2-chloromethyloxazine[1] **1** (44.1 g, 0.25 mol) and triphenylphosphine (91 g, 0.35 mol) in benzene (500 ml) was heated with stirring at reflux for 32 hr. The mixture was cooled, and the salt was filtered, washed

Table II
Elemental Analysis for Vinyl Oxazines 5

R_1	R_2	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
Ph	H	78.56	8.35	6.11	78.46	8.62	6.03
Ph	Me	78.97	8.70	5.76	78.68	8.65	5.86
Ph	Ph	82.59	7.59	4.59	82.54	7.62	4.71
Me	Me	72.88	10.56	7.73	72.99	10.76	7.65
Et	H	72.88	10.56	7.73	72.74	10.54	7.83
n-Hex	H	75.90	11.46	5.90	75.63	11.50	5.86
$-(CH_2)_4-$		75.32	10.21	6.76	75.48	10.06	6.80
2-C_5H_4N	H	73.01	7.88	12.16	72.85	7.61	11.92

three times with dry ether, and dried under vacuum. The reaction gave 77 g (70%) of **2**. The product could be recrystallized from acetonitrile–ether: mp 224°; uv (EtOH) 273, 267, 263 nm; ir (KBr) 1603 cm^{-1}; nmr ($CDCl_3$) δ 7.45 (m, 15), 4.22 (d, 0.85, J = 15 Hz, exchanges with D_2O), 10.2 (b, 0.85, exchanges with D_2O), 1.42 (d, 6), 0.81 (d, 3).

Anal. Calcd for $C_{25}H_{29}NPCl$: C, 70.50; H, 6.86; N, 3.29. Found: C, 70.63; H, 6.76; N, 3.24.

Vinyl Oxazines 5 from Oxazine Phosphonium Salt 2. The phosphonium chloride **2** (8.76 g, 0.02 mol) was suspended in THF (35 ml) and to this suspension was added freshly sublimed potassium *tert*-butoxide (2.24 g, 0.02 mol). A yellow solution of the phosphorane **4** formed immediately. The solution showed uv absorption at 342 nm and was used in the subsequent reactions.

Aldehydes were added dropwise to the solutions prepared above and the mixture was allowed to stir for 4 hr (ketones were refluxed for 18 hr). The mixture was poured into water, made acidic (pH ~3), and extracted with benzene and the benzene extracts were discarded. The aqueous acid solution was neutralized with sodium bicarbonate and extracted with ether. The ether solution was concentrated and the residue was applied to a neutral alumina column (Woelm, activity I) and eluted with ether–pentane (1:1). Yields and pertinent data are listed in Table I. Elemental analyses are given in Table II.

2-Trideuteriomethyl-4,4,6-trimethyl-5,6-dihydro-1,3-oxazine (7b). Phosphonium salt **2** (8.75 g, 0.02 mol) was added to D_2O (20 ml) and the suspension was allowed to stir for 30 min. Ten milliliters of 20% NaOD in D_2O was added and the mixture was allowed to stir for 15 min. The product was extracted with ether–pentane (1:3) and dried over potassium carbonate. The extracts were evaporated and the residue was distilled to give 2.2 g (70%) of **7b**: bp 47° (17 mm); ir 2220, 1660 cm^{-1}; m/e 144. The methyl singlet at δ 1.77 was barely visible.[4]

2-(Diethylphosphonomethyl)-4,4,6-trimethyl-5,6-dihydro-1,3-oxazine (3b). The chloromethyloxazine **1** (44.1 g, 0.25 mol) was added to triethyl phosphite (100 g) and the solution was refluxed vigorously for 24 hr. The solution was then distilled under vacuum (0.1 mm) and the oxazine phosphonate **3b**, bp 109° (0.075 mm), was collected. The reaction gave 55 g (80%) of a pale yellow liquid: ir 1660, 1260, 1050, 960 cm^{-1}; nmr (CCl_4) δ 3.8–4.4 (m, 5), 2.6 (d, 2, J = 21 Hz), 1.8 (d of t, 2), 1.3 (t, 6), 1.2 (d, 3), 1.1 (s, 6).

Anal. Calcd for $C_{12}H_{24}NO_4P$: C, 51.99; H, 8.73; N, 5.06. Found: C, 52.01; H, 8.70; N, 5.12.

2-(Dimethylphosphonomethyl)-4,4,6-trimethyl-5,6-dihydro-1,3-oxazine (3a) was prepared as described above using trimethyl phosphite. The reaction gave **3a** in 45% yield: bp 102° (1 mm); mp 56–57° [petroleum ether (bp 30–60°)]; ir 1660, 1260 cm^{-1}; nmr (CCl_4) δ 4.2 (m, 1), 3.8 (d, 6, J = 12 Hz), 2.6 (d, 2, J = 22 Hz), 1.7 (d of t, 2), 1.4 (d, 3), 1.2 (s, 6).

Anal. Calcd for $C_{10}H_{20}NO_4P$: C, 48.20; H, 8.10; N, 5.62. Found: C, 47.98; H, 8.22; N, 5.48.

Vinyl Oxazines 5 from Oxazine Phosphonate 3b. Oxazine phosphonate **3b** (5.54 g, 0.02 mol) was added to a stirred suspension of sodium hydride (1.0 g of a 56% dispersion, 0.022 mol) in 30 ml of 1,2-dimethoxyethane (DME). The evolution of hydrogen at 25° was complete after 2.5 hr and the resulting yellow solution was treated with 0.22 mol of aldehyde or ketone. Stirring was continued for 4 hr at room temperature, the mixture was poured into ice–water, acidified (1 *N* HCl), and extracted with petroleum ether, and the extracts were discarded. The aqueous solution was made basic (pH ~9) and the vinyl oxazine **5** was recovered by ether extraction, concentration, and distillation (*cf.* Table I).

Phosphonium Salt 10. A solution of 19.0 g (0.1 mol) of **9**[1] and 35 g (0.13 mol) of triphenylphosphine in 150 ml of xylene was heated to reflux for 48 hr. Isolation of **10** was accomplished as previously described for **2**. The salt **10**, mp 241° (acetonitrile–ether), was formed in 45% yield (18.0 g): ir (KBr) 1600 cm^{-1}; nmr ($CDCl_3$) δ 9.0 (b, exchangeable with D_2O), 5.2 (b, exchangeable with D_2O), 7.4–8.2 (m, 15).

Anal. Calcd for $C_{27}H_{31}NOPCl$: C, 71.74; H, 6.91; N, 3.10. Found: C, 71.80; H, 6.99; N, 3.27.

Phosphonate 11. The sodium salt of **3b** prepared as above was treated with 1 equiv of methyl iodide and the mixture was stirred overnight. The mixture was poured into water and extracted with ether. Evaporation and distillation gave **11** (89%): bp 97° (0.1 mm); ir (film) 1660, 1260 cm^{-1}; nmr (CCl_4) δ 4.1 (m, 5), 2.5 (m, 1, J = 23 Hz), 1.1–1.8 (m, 20).

Anal. Calcd for $C_{13}H_{26}NO_4P$: C, 53.60; H, 9.00. Found: C, 53.92; H, 9.22.

2-(1-Phenylpropen-2-yl)-4,4,6-trimethyl-5,6-dihydro-1,3-oxazine (8) was prepared from phosphonium salt **2** in 78% yield and from phosphonate **3b** in 75% yield according to the procedures already outlined using these reagents: bp 80° (0.05 mm); uv (EtOH) 261 nm (ϵ 20,000); ir (film) 1620, 1635 cm^{-1}; nmr (CCl_4) δ 7.3 (s, 6), 4.1 (m, 1), 2.0 (d, 3, J = 1.5 Hz), 1.7 (d of t, 2), 1.4 (d, 3), 1.1 (s, 6).

Anal. Calcd for $C_{16}H_{21}NO$: C, 78.97; H, 8.70; N, 5.76. Found: C, 79.00; H, 8.55; N, 5.73.

Oxazine Phosphonate 12. The sodium salt of **3b** was prepared in the manner described for the preparation of **11** except that 2.5 equiv of sodium hydride was employed. Addition of 2.5 equiv of methyl iodide followed and the solution was stirred overnight. The reaction gave **12** in 93% yield: bp 110° (0.5 mm); ir (film) 1660, 1260 cm^{-1}; nmr (CCl_4) δ 4.05 (m, 1), 4.95 (pentet, 4), 1.6 (d of t, 2), 1.4 (d, 3), 1.3 (t, 6), 1.1 (s, 6), 1.15 (s, 6).

Anal. Calcd for $C_{14}H_{28}NO_4P$: C, 55.07; H, 9.25; N, 4.59. Found: C, 54.96; H, 9.33; N, 4.80.

Diethyl 1-Formyl-1-methylethylphosphonate (36). Reduction of the oxazine phosphonate **12** using sodium borohydride (−45°, pH 5–7) as previously described[4] followed by heating in oxalic acid (2 hr) gave an aqueous mixture which was extracted with ether. Distillation of the ether residue gave **36** in 65% yield: bp 62° (0.4 mm); ir (film) 2720, 1720, 1250 cm^{-1}; nmr (CCl_4) δ 9.6 (d, 1, J = 2 Hz), 4.1 (pentet, 4), 1.4–1.2 (d, t, 12).

Anal. Calcd for $C_8H_{17}PO_4$: C, 46.15; H, 8.24. Found: C, 46.20; H, 8.00.

Aldehydes from Vinyl Oxazines 5. The following aldehydes were prepared from the indicated vinyl oxazine **5** by the general borohydride reduction–oxalic acid hydrolysis procedures described previously[4] on a 40-mmol scale.

Cinnamaldehyde (14) was prepared in yields of 50–75% from **5** (R_1 = Ph; R_2 = H). Yields appeared to be dependent upon the pH of the borohydride reduction step. The pH was varied in several runs from 5 to 9. Best results were obtained with an apparent pH of 7. The product formed a semicarbazone, mp 206–207° (lit.[7] mp 208°).

3-(2-Pyridyl)acrolein (15) was prepared in 45% yield from **5** (R_1 = C_5H_5N; R_2 = H). The product was isolated by neutralization of the oxalic acid solution with sodium bicarbonate and extraction of the product with ether. The product **15** had mp 42° (hexane) (lit.[8] mp 43°); ir (film) 2760, 1670 cm^{-1}.

2-Methyl-3-phenylacrolein (16) was prepared from **8** in 65% yield. The product formed a semicarbazone, mp 207° (lit.[7] mp 207–208°).

A 50:50 Mixture of 2-Nonenal (17) and Nonanal (18) was prepared from **5** (R_1 = R_2 = H) in 61% yield. The products were collected from vpc using 10% SE-31 on Diatoport S at 100° and identified by the melting points of their respective 2,4-dinitrophenylhydrazones. 2-Nonenal[7] and nonanal[7] gave derivatives which melted at 126 and 106°, respectively.

Reduction of 5 (R_1 = R_2 = Me) to 22. Treatment of 3.62 g (0.02 mol) of **5** with aqueous sodium borohydride (−45°, pH 5–7) according to the standard procedure[4] gave, after extraction with ether, 3.43 g (94%) of **22**: bp 80° (0.3 mm); ir (film) 3260 cm^{-1}; nmr (CCl_4) δ 5.2 (t, 1), 3.9 (m, 1), 3.1 (d, 2), 1.6 (s, 3), 1.7 (s, 3), 0.9–1.5 (d, s, m, 13); NH, OH protons exchangeable with D_2O were masked in the latter region of the spectrum.

Anal. Calcd for $C_{11}H_{23}NO$: C, 71.30; H, 12.51; N, 7.56. Found: C, 71.01; H, 12.49; N, 7.80.

***N*-Methyl Salts 24a and 24b (R_1 = H; R_2 = Ph). A. Methiodide 24a.** Treatment of **5** (R_1 = H; R_2 = Ph) with excess methyl iodide in a small amount of ether with gentle warming for 18 hr in the dark resulted in a 96% yield of **24a**. The product was washed with ether for use in subsequent reactions. Recrystallization from acetonitrile–ether resulted in yellow needles, mp 223–224°, ir 1590, 1635 cm^{-1}.

Anal. Calcd for $C_{16}H_{22}NOI$: C, 51.76; H, 5.97; N, 3.77. Found: C, 52.06; H, 6.12; N, 3.85.

B. Methyl Fluoroborate 24b. Treatment of **5** (R_1 = H; R_2 = Ph) with 1.5 equiv of trimethyloxonium fluoroborate in methylene chloride cooled to 0° for 30 min resulted in a 93% yield of the salt, which was isolated by filtering the methylene chloride solution, removal of the solvent, and recrystallizing from acetonitrile–ether to give colorless plates, mp 164°, ir 1590, 1634 cm^{-1}.

Anal. Calcd for $C_{16}H_{22}NOBF_4$: C, 58.03; H, 6.70; N, 4.23. Found: C, 57.99; H, 6.52; N, 4.53.

***N*-Methyl Salt 24a (R_1 = R_2 = Me).** The salt was prepared as above using excess methyl iodide and crystallized in quantitative yield. The salt was recrystallized from acetonitrile–ether to give colorless needles, mp 202°, ir 1574, 1625 cm^{-1}.

Anal. Calcd for $C_{12}H_{22}NOI$: C, 44.59; H, 6.87; N, 4.33. Found: C, 44.65; H, 6.90; N, 4.37.

Reduction of *N*-Methyl Salt 24a (R_1 = R_2 = Me) with Sodium Borohydride at 0°. The methiodide salt **24a** (6.46 g, 0.02 mol) was dissolved in absolute methanol (20 ml) and the solution was cooled to −30°, and to this solution was added, dropwise, sodium borohydride (0.02 mol) dissolved in a minimum amount of water. The solution was allowed to warm to 0° during a 1-hr period, 50 ml of cold water was added, the product was extracted with ether, and the ether extracts were washed with brine and dried (Na_2SO_4). Evaporation and distillation of the residue gave 5.41 g (90%) of **27**: bp 50° (0.05 mm); ir 3220 cm^{-1}; nmr (CCl_4) δ 5.9 (br s, 1, exchangeable with D_2O), 5.2 (t, 1), 4.0 (m, 1), 3.1 (m, 2), 2.2 (s, 3), 1.7 (s, 3), 1.8 (s, 3).

Anal. Calcd for $C_{12}H_{25}NO$: C, 72.31; H, 12.64; N, 7.03. Found: C, 72.28; H, 12.63; N, 6.79.

Reduction of *N*-Methyl Quaternary Salts 24a and 24b. Preparation of Aldehydes 14 and 26. The following *N*-methyl tetrahydrooxazines **25** were prepared by reduction of the corresponding *N*-methyl salts using sodium borohydride in methanol. The methanol solution was cooled (−45 to −35°) and this temperature was maintained throughout the reaction (30 min). Excess borohydride was destroyed at −45° by the addition of dilute hydrochloric acid. The solution was then made basic and the product was isolated by ether extraction. Drying and concentration of the extracts followed by distillation furnished the products.

The tetrahydrooxazine **25** (R_1 = H; R_2 = Ph) was prepared from **24a** (98%, 85% distilled) and from **24b** (93%): bp 95° (0.05 mm); ir 3100–3480, 1628, 1600 cm^{-1}; nmr (CCl_4) δ 7.0–7.6 (m, 5), 5.8 (d of d, 1), 6.7 (d, 1), 4.8 (d, 1), 3.8 (m, 1), 2.2 (s, 3), 0.8–1.8 (m, 11).

Anal. Calcd for $C_{16}H_{23}NO$: C, 78.32; H, 9.45; N, 5.71. Found: C, 78.26; H, 9.33; N, 5.46.

The product was hydrolyzed to cinnamaldehyde using aqueous oxalic acid (reflux 2 hr) in 78% yield.

The tetrahydrooxazine **25** (R_1 = R_2 = Me) was prepared from **24a** (95%). The crude product **25** was hydrolyzed to 3-methyl-2-butenal (**26**) by oxalic acid in 65% yield. The aldehyde **26** formed a semicarbazone, mp 222° (methanol) (lit.[7] mp 221–222°).

Preparation of Ketones 29 from *N*-Methyl Salts of Vinyl Oxazines 24. To a suspension of the *N*-methyl iodide or fluoroborate (0.02 mol) in 20 mol of THF cooled to 0° was added a solution of the organometallic reagent (Grignard reagent or organolithium reagent, 0.022 mol) by drops; 2 hr was allowed for complete reaction. The solution was poured onto ice and then extracted with ether. The ether extracts were dried (K_2CO_3) and evaporated to give the intermediate **28** which was directly subjected to oxalic acid cleavage as described previously.

The following ketones were prepared by this general procedure from the indicated starting materials.

4-Phenyl-2-buten-2-one (29a) was prepared from methyllithium and **24a** (R_1 = H; R_2 = Ph) as described above in 82% yield. The product formed a semicarbazone, mp 176° (lit.[7] mp 177.5°).

4,4-Dimethyl-1-phenyl-1-penten-3-one (29c) was prepared from *tert*-butyllithium (solution in pentane) and **24a** (R_1 = H; R_2 = Ph) in 20% yield. The product had mp 43° (lit.[7] mp 43°).

5-Methyl-4-hexen-3-one (29b) was prepared from ethyllithium and **24a** (R_1 = R_2 = Me) in 55% yield. The product formed a semicarbazone, mp 160° (ethanol–water) (lit.[7] mp 162°).

4-Cyclopentylidine-3-butanone (29d) was prepared from **5** [R_1 = R_2 = $-(CH_2)_4-$] by preparing, *in situ*, the *N*-methiodide salt **24a**, removing the excess methyl iodide *in vacuo*, and addition of a solution of ethyllithium in THF. The crude adduct **25** was hydrolyzed without further purification to the ketone **29d** (55%), bp 96° (20 mm), semicarbazone mp 171° (lit.[9] mp 170–171°).

Preparation of Carboxylic Acids 35 from *N*-Methyl Salts of Vinyl Oxazines 24a. The methiodide salts **24a** were dissolved in cold water and the solution was rendered alkaline (pH ~10). After stirring for 10 min, the solutions were heated to reflux (3–4 hr) and reacidified. Extraction of the aqueous solution with ether afforded the carboxylic acids **35**. In this fashion β,β-dimethylacrylic acid (**35a**, 68%, mp 70°), cinnamic acid (**35b**, 92%, mp 131°), and cyclopentylideneacetic acid (**35c**, 87%, mp 64°) were obtained.

Amino Ester 34 (R_1 = R_2 = Me). The methiodide salt **24a** (6.46 g, 0.02 mol) was dissolved in cold water (25 ml) and the solution was made basic (pH ~10) for 10 min. The product was extracted with ether, and the ether extracts were dried (K_2CO_3) and evaporated to give on distillation 3.93 g (92%) of **34**, bp 75° (0.1 mm), ir 1710, 1650 cm^{-1}.

Anal. Calcd for $C_{12}H_{23}NO_2$: C, 67.57; H, 10.87; N, 6.57. Found: C, 67.54; H, 11.03; N, 6.77.

On heating in aqueous dilute sodium hydroxide (1.5 *N*) for 4 hr, the amino ester produced β,β-dimethylacrylic acid (**35a**) in 80% yield.

Acknowledgment. The authors are grateful to the National Science Foundation (GP 22541), the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the National Institutes of Health for financial support of this work. Generous supplies of organolithium reagents from the Lithium Corp. of America are also gratefully acknowledged.

Registry No.—**1**, 50259-03-5; **2**, 50259-42-2; **3a**, 50259-43-3; **3b**, 50431-01-1; **5** (R_1 = Ph; R_2 = H), 50259-44-4; *cis*-**5** (R_1 = Ph; R_2 = Me), 50259-45-5; *trans*-**5** (R_1 = Ph; R_2 = Me), 50259-46-6; **5** (R_1 = R_2 = Ph), 50259-47-7; **5** (R_1 = R_2 = Me), 50259-48-8; **5** (R_1 = Et; R_2 = H), 50259-49-9; **5** (R_1 = *n*-Hex; R_2 = H), 50259-50-2; **5** [R_1, R_2 = $-(CH_2)_4-$], 50259-51-3; **5** (R_1 = 2-C_5H_4N; R_2 = H), 50259-52-4; **7b**, 50259-53-5; **8**, 50259-54-6; **9**, 50259-07-9; **10**, 50259-56-8; **11**, 50259-57-9; **12**, 50259-58-0; **17** 2,4-DNPH, 18287-00-8; **18** 2,4-DNPH, 2348-19-8; **22**, 43152-87-0; **24a** (R_1 = H; R_2 = Ph), 50259-62-6; **24a** (R_1 = R_2 = Me), 50259-63-7; **24b** (R_1 = H; R_2 = Ph), 50262-97-0; **25** (R_1 = H; R_2 = Ph), 50546-26-4; **27**, 50259-64-8; **29d**, 50259-65-9; **34** (R_1 = R_2 = Me), 50259-66-0; **36**, 35078-65-0.

References and Notes

(1) Part XXIII of a study on 5,6-dihydro-1,3-oxazines. For previous papers in this series see G. R. Malone and A. I. Meyers, *J. Org. Chem.*, **39**, 618 (1974).
(2) Address all correspondence to this author at the Department of Chemistry, Colorado State University, Fort Collins, Colo. 80521.
(3) We thank Professor L. M. Trefonas of Louisiana State University in New Orleans for this determination. The details of this work will be published elsewhere. The projection formula and data for bond lengths and angles may be found in the Ph.D. Thesis of G. R. Malone, Wayne State University, 1972.
(4) A. I. Meyers, A. Nabeya, H. W. Adickes, I. R. Politzer, G. R. Malone, A. C. Kovelesky, R. L. Nolen, and R. C. Portnoy, *J. Org. Chem.*, **38**, 36 (1973).
(5) A. I. Meyers and N. Nazarenko, *J. Amer. Chem. Soc.*, **94**, 3243 (1972).
(6) A. I. Meyers and N. Nazarenko, *J. Org. Chem.*, **38**, 175 (1973).
(7) I. Heilbron, "Dictionary of Organic Compounds," Oxford University Press, New York, N. Y. 1965.
(8) M. Ohta and Y. Isowa, *Nippon Kagaku Zasshi*, **80**, 688 (1959).
(9) A. H. Dickins, W. E. Hugh, and G. A. R. Kon, *J. Chem. Soc.*, 572 (1929).

Hydrogenation of 4-(3,5-Dimethyl-4-isoxazoylmethyl)-7,7a-dihydro-1β-hydroxy-7aβ-methyl-5(6H)-indanone

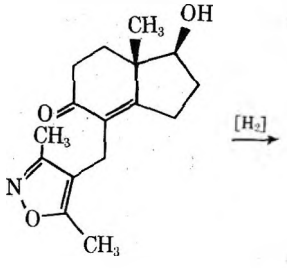
Thomas C. McKenzie[1]

Department of Chemistry, Columbia University, New York, New York 10027

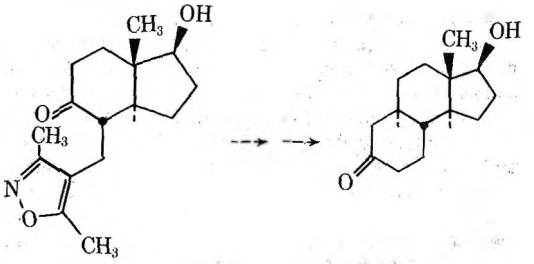
Received October 12, 1973

The hydrogenation of the title compound was reinvestigated and the major product was reassigned the trans configuration. The structure assignment was based on a single-crystal X-ray study of 6α-bromo-4α-(3,5-dimethyl-4-isoxazoylmethyl)-1β-hydroxy-7aβ-methyl-3aα,6,7,7a-tetrahydro-5(4H)-indanone (3). The bromo compound 3 crystallizes in the tetragonal space group $P4_2/nbc$ with $a = b = 15.6134$ and $c = 27.8258$ Å. The structure was solved by the heavy atom method and refined to an R index of 11.2%. A rationalization of the stereochemical outcome of the hydrogenation of hydrindanones is offered.

The production of a trans CD ring juncture has been a serious problem in the efficient total synthesis of steroids. While studying the utility of the isoxazole annelation sequence[2] for steroid synthesis we hoped to overcome this problem by hydrogenating the hydrindanone isoxazole **1**. If the enone **1** could be stereospecifically reduced to the trans bicyclic ketone **2**, then the isoxazole ring could easily be converted into the B ring of a de-A steroid with the natural configuration.



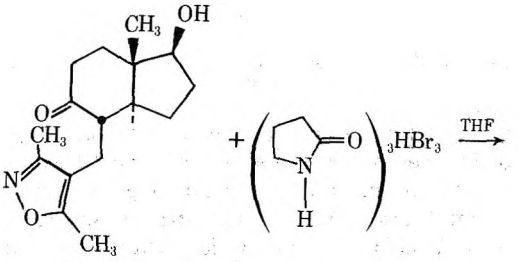
1



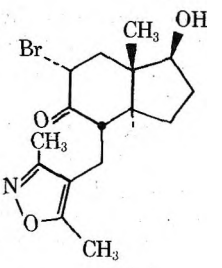
2

Hydrogenation of **1** over palladium on charcoal in acidic ethanol gave an 85:15 mixture of two reduced ketones, **2a** and **2b**. These two ketones exhibited angular methyl group resonances at δ 1.09 and 1.25, respectively, in the nmr. This hydrogenation had been studied previously by McMurry,[3] and he had assigned ketone **2b**, the δ 1.25 compound, to the trans series on the basis of the half-width of its angular methyl group signal in the nmr.[4] This assignment seemed unlikely because the Zürcher[5] rules predict that the trans ketone should exhibit an angular methyl resonance δ 0.091 upfield from that of the cis ketone and because there was precedent which suggested that 4-substituted hydrindanones should give 30–80% trans product.[6]

In fact, both reduced ketones, **2a** and **2b**, exhibited similar, wide, angular methyl group resonances in the nmr ($\Delta W_h/2 = 0.75$ and 0.65 Hz, respectively). Stereochemistry could be assigned, with confidence, only after the X-ray crystal structure of the bromo ketone **3** had been completed. The bromo ketone **3** was prepared by PHT bromination[7] of **2a**, which in turn was isolated from the hydrogenation mixture by repeated fractional crystallization.



2a

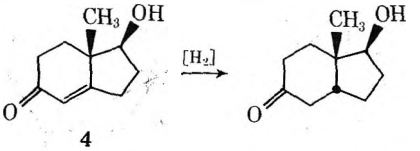


3

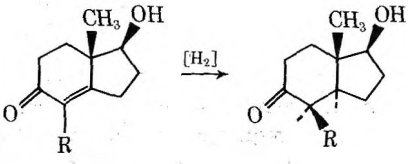
The X-ray data from **3** were collected with nickel-filtered Cu Kα radiation to a spacing of 0.94 Å. The structure was solved by the Patterson method and refined by full-matrix least-squares refinement with anisotropic temperature factors of all nonhydrogen atoms. The R index is 11.2%. A view of the molecule is shown in Figure 1 and reveals that bromo ketone **3** and therefore **2a** have the trans configuration and not the cis assigned by McMurray.

Discussion

The effect of a substituent at C-4 on the stereochemistry of hydrindanone hydrogenation is a curious phenomenon. The parent enone without a side chain at C-4 (**4**) gives largely the cis product upon reduction,[8] while substituted hydrindanones (**5**) give considerably more of the trans product. The amount of trans product is roughly[6] correlated with the size of the side chain.



4



5

The classical Horiuti–Polanyi[9] mechanism of hydrogenation requires that the two hydrogen atoms add to the

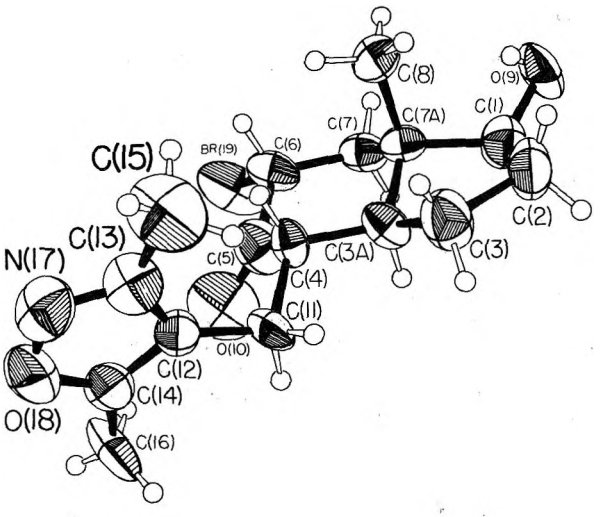
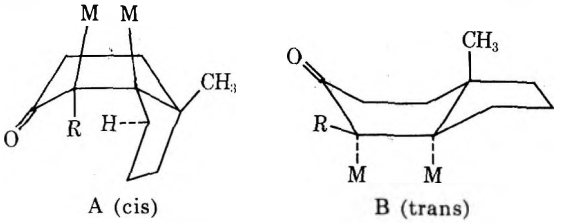


Figure 1. ORTEP drawing of the bromo ketone 3.

same side of an olefin. In the case of a substituted hydrindanone 5 this means that the side chain must become axial in the trans product unless there is a prereduction double-bond equilibration. We did not observe any axial product under our acidic hydrogenation conditions, but Baggaley[10] has reported that hydrogenation of a hydrindanone with a methoxy group at C-4 (5, R = OCH_3) under neutral, nonequilibrating conditions did give a trans product with an axial methoxy group. The question, then, is why a side chain at C-4 leads to the production of more of the product with the least stable ring junction, especially when this requires the side chain to become axial.

Part of the answer is that the hydrogenation of 4 and 1 may have different product-determining steps. Unlike 4, the hydrogenation of 1 exhibits no pressure effect on the stereochemistry of the product.[9c] This suggests that the slow step in the hydrogenation of 1, the tetrasubstituted olefin, is the formation of the adsorbed olefin[11] and not the formation of the half-hydrogenated state. The stereochemical results than can be rationalized in terms of a boat-like complexed olefin.[12]

There are two plausible boat complexes, A and B, each leading to a different product. Addition of hydrogen in some fashion[13] to the cis boat A will give a cis saturated ketone. However, if the R group is large, steric repulsion between the side chain and the 3α hydrogen atom in the cis boat A will favor the trans boat B. Transfer of hydrogen and desorption of B gives a trans boat saturated ketone with an equatorial side chain. Ring inversion then gives the trans chair axial product. In the case of 1, the first-formed trans chair axial product is presumably equilibrated under the acidic reaction conditions to the observed trans chair equatorial product.



M stands for a metal surface atom

The boat intermediate may well be a consequence of the stereoelectronic requirement that the two carbon–metal bonds be eclipsed and coplanar in the olefin complex.[14] Hussey[15] has pointed out that this eclipsing of carbon–metal bonds during the hydrogenation of simple, isolated, cyclohexene double bonds implies a boat intermediate, and he has offered some evidence that is consistent with this suggestion, at least for simple cyclohexenes hydrogenated over a platinum catalyst.

Experimental Section

Preparation of 4α-(3,5-Dimethyl-4-isoxazolylmethyl)-1β-hydroxy-7aβ-methyl-3aα,6,7,7a-tetrahydro-5-(4*H*)-indanone (2a). A solution of 50 mg (0.182 mmol) of isoxazole alcohol 1 in 0.01 *M* perchloric acid in ethanol and 15 mg of 10% palladium on charcoal was stirred for 48 hr under 1 atm of hydrogen. Solid sodium bicarbonate was added, and the mixture was swirled for 5 min. Filtration and evaporation gave 49 mg (0.177 mmol, 97.5% yield) of a semisolid material identified as an 85:15 mixture of trans and cis hydrindanone. Recrystallization from hexane–isopropyl ether gave a purer sample of **2a**: mp 146–149°; nmr ($CDCl_3$) δ 3.73 (m, 1 H), 2.73 (s, 3 H), 2.21 (s, 3 H), 1.09 (s, 3 H); ir ($CHCl_3$) 3.03, 5.89, 6.10, 9.02, 11.18 μ; mass spectrum (25 eV) *m/e* (rel intensity) 277 (9.5), 150 (5.1), 110 (100).

Preparation of 6α-Bromo-4α-(3,5-dimethyl-4-isoxazolylmethyl)-1β-hydroxy-7aβ-methyl-3aα,6,7,7a-tetrahydro-5(4*H*)-indanone (3). A solution of 22.5 mg (0.081 mmol) of ketone **2a** and 46.8 mg (0.094 mmol) of pyrrolidone 2-hydrotribromide (PHT) in 4 ml of THF was allowed to stand at room temperature for 4 hr. The solution was filtered from the precipitate which had formed, and the filtrate was evaporated at reduced pressure to give 47 mg of crystalline material. The crude product was chromatographed on a 10 × 20 × 0.2 cm silica gel plate, developed with 60:40 ethyl acetate–chloroform (R_f 0.35) to yield 9.4 mg (0.026 mmol, 32.6%) of colorless crystals. Recrystallization from acetone–hexane gave crystals suitable for X-ray: mp 161–164°; nmr ($CDCl_3$) δ 2.42 (s, 3 H), 2.23 (s, 3 H), 1.18 (s, 3 H); ir ($CHCl_3$) 2.77, 5.77, 6.10 μ.

X-Ray Structure of 3. Unit cell dimensions were obtained from least-squares refinement of the 2θ angles of 31 reflections measured on a Datex automated General Electric diffractometer. Unit cell parameters are $a = b = 15.6134 \pm 0.0002$ Å; $c = 27.8258 \pm 0.0004$ Å.

The absence of *hk*0 reflections for $h + k$ odd, 0*kl* reflections for *k* odd, and *hhl* reflections for *l* odd indicated that the space group is $P4_2/nbc$. The crystal density was found to be 1.41 ± 0.01 g cm^{-3}. The calculated density is 1.40 g cm^{-3} for 16 molecules of molecular weight 356.261 per unit cell.

Intensity data were collected by the θ–2θ scan method with nickel-filtered Cu Kα radiation (λ = 1.5418 Å). Reflections were collected to a maximum value of 2θ = 110° with a scan rate in 2θ of 2° min^{-1}. Three reflections, the 201, 224, and 220, monitored at regular intervals during the data collection, decayed in intensity by 5.3, 7.9, and 3.4 standard deviations, respectively.

The intensities of 2140 reflections were measured. The intensities of 339 of these were observed to be less than one standard deviation above background and were assigned a value of zero with zero weight throughout the refinement. The data were corrected for Lorentz–polarization effects and for crystal decay but not for absorption ($\mu = 37$ cm^{-1}). The data were placed on an absolute scale by Wilson's method.[16] A Howells, Phillips, and Rogers plot[17] confirmed that the crystal is centrosymmetric.

Approximate coordinates of the nonhydrogen atoms were obtained by the Patterson–Fourier process. Least-squares refinement of coordinates and anisotropic temperature factors converged at an *R* index of 11.2%. The weighted *R* index was 4.7%, and the goodness of fit was 4.2. The average standard deviation in atomic position is 0.01 Å, the average standard deviation in bond length is 0.02 Å, and the average standard deviation in bond angle is 1°.[18]

Acknowledgment. The author wishes to thank Professor Gilbert Stork for encouragement and guidance. The financial support of the National Institutes of Health is gratefully acknowledged.

Registry No.—1, 50323-79-0; 2a, 50323-80-3; 3, 50323-81-4.

Supplementary Material Available. Tables I–V, containing the observed and calculated structure factors, the heavier atom parameters, the hydrgen atom coordinates, the bond distances and angles, and the least-square plane of the isoxazole ring, respectively, will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary

material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-74-629.

References and Notes

(1) (a) Postdoctoral Fellow of the National Institutes of Health. (b) Address correspondence to Department of Chemistry, California Institute of Technology, Pasadena, Calif. 91109.
(2) G. Stork, S. Danishefsky, and M. Ohashi, *J. Amer. Chem. Soc.*, **89**, 5459 (1967).
(3) J. E. McMurry, Ph.D. Thesis, Columbia University, New York, N. Y., 1967.
(4) (a) M. J. T. Robinson, *Tetrahedron Lett.*, 1685 (1965); (b) K. L. Williamson, T. Howell, and T. A. Spencer, *J. Amer. Chem. Soc.*, **88**, 325 (1966).
(5) R. F. Zürcher, *Helv. Chim. Acta*, **46**, 2054 (1963).
(6) (a) G. Nomine, G. Amiard, and V. Torelli, *Bull. Soc. Chim. Fr.*, 3664 (1968); (b) L. Velluz, G. Nomine, G. Amiard, V. Torelli, and J. Cerede, *C. R. Acad. Sci.*, **257**, 3086 (1963); (c) G. H. Douglas, J. M. H. Graves, D. Hartley, G. A. Hughes, B. J. McLoughlin, J. Siddall, and H. Smith, *J. Chem. Soc.*, 5072 (1963); (d) O. I. Fedorova, G. S. Grinenko, and V. I. Maksimov, *J. Org. Chem. USSR*, **4**, 600 (1968); *Dokl. Chem.*, **171**, 1154 (1966); (e) Z. G. Hajos, D. R. Parrish, and E. P. Oliveto, *Tetrahedron Lett.*, 6495 (1966).
(7) D. V. C. Awang and S. Wolfe, *Can. J. Chem.*, **47**, 706 (1969).
(8) (a) C. B. C. Boyce and J. S. Whitehurst, *J. Chem. Soc.*, 4547 (1960); (b) K. H. Baggaley, S. G. Brooks, J. Green, and B. T. Redman, *J. Chem. Soc. C*, 2671 (1971); (c) T. C. McKenzie, Ph.D. thesis, Columbia University, New York, N. Y., 1971.
(9) I. Horiuti and M. Polanyi, *Trans. Faraday Soc.*, **30**, 1164 (1934).
(10) K. H. Baggaley, S. G. Brooks, J. Green, and B. T. Redman, *J. Chem. Soc. C*, 2673 (1971).
(11) S. Siegel, *Advan. Catal.*, **16**, 123 (1966).
(12) There is a second possible explanation for the stereochemical results. Hydrindanone **4** may undergo a prereduction α,β-β,γ double bond equilibration and the β,γ unsaturated ketone could undergo fast reduction to give predominantly a cis product. At higher hydrogen pressure this isomerization would be intercepted, resulting in formation of more of the trans product. In the case of C-4 substituted hydrindanones like **1** the α,β double bond isomer would be significantly more stable than the β,γ isomer and again more of the trans product would be formed. That the β,γ isomer does not give predominantly the cis product was shown by reducing **4** with deuterium and exchanging all the lable hydrogens with H_2O. Mass spectra showed that the separated cis and trans products had equal amounts of retained deuterium.
(13) R. L. Augustine, D. C. Migliorini, R. E. Foscante, C. S. Sodano, and M. J. Sisbarro, *J. Org. Chem.*, **34**, 1075 (1969).
(14) R. L. Burwell, B. K. C. Shim, and H. C. Rowlinson, *J. Amer. Chem. Soc.*, **79**, 5142 (1957).
(15) J. F. Sauvage, R. H. Baker, and A. S. Hussey, *J. Amer. Chem. Soc.*, **82**, 6090 (1960).
(16) A. J. C. Wilson, *Nature (London)*, **150**, 152 (1942).
(17) E. R. Howells, D. C. Phillips, and D. Rogers, *Acta Crystallogr.*, **3**, 210 (1950).
(18) See paragraph at end of paper regarding supplementary material.

Quinoxaline Studies. XXI.[1a] 1,4-Bis(*p*-toluenesulfonyl)-2-hydroxymethyl-1,2,3,4-tetrahydroquinoxaline

George H. Fisher[1b] and Harry P. Schultz*

Department of Chemistry, University of Miami, Coral Gables, Florida 33124

Received August 2, 1973

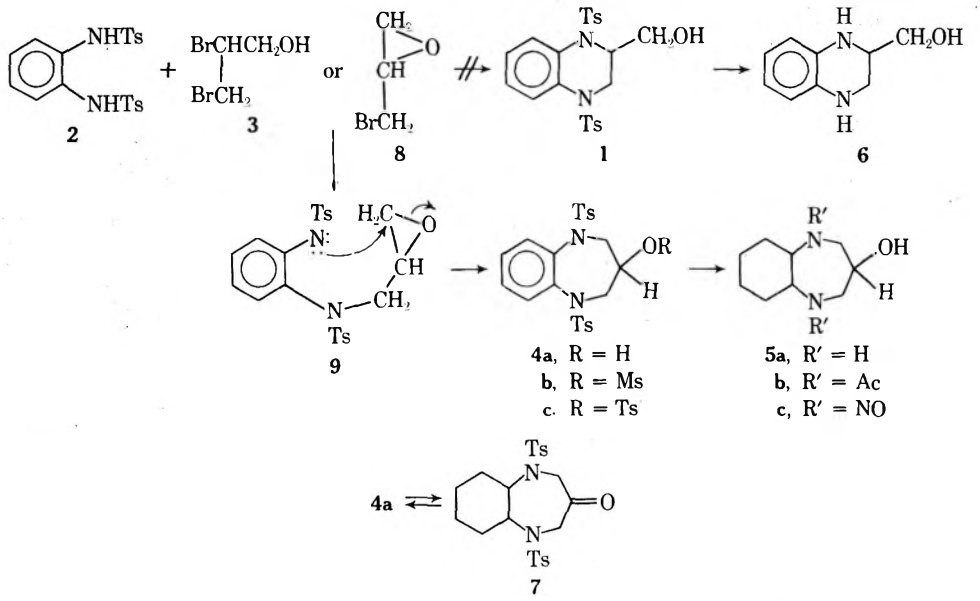
The alcohol originally reported by Acheson as 1,4-bis(*p*-toluenesulfonyl)-2-hydroxymethyl-1,2,3,4-tetrahydroquinoxaline (**1**) is 1,5-bis(*p*-toluenesulfonyl)-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-3-ol (**4a**). Alcohol **1** has been prepared by condensation of *N,N'*-bis(*p*-toluenesulfonyl)-o-phenylenediamine with methyl 2,3-dibromopropionate to give 1,4-bis(*p*-toluenesulfonyl)-2-carbomethoxy-1,2,3,4-tetrahydroquinoxaline (**14**), which was reduced with lithium aluminum hydride to give authentic **1**. Detosylation of alcohol **1** with sulfuric acid gave 2-hydroxymethyl-1,2,3,4-tetrahydroquinoxaline (**6**), identical with that obtained by lithium aluminum hydride reduction of 2-carboethoxy-1,2,3,4-tetrahydroquinoxaline (**15**). Similarly, detosylation of diazepinol **4a** with sulfuric acid gave 2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-3-ol (**5a**), which could be retosylated to give diazepinol **4a**.

Substituted tetrahydroquinoxalines are of interest as models for tetrahydrofolic acid.[2,3] Therefore, the reported[4] synthesis of 1,4-bis(*p*-toluenesulfonyl)-2-hydroxymethyl-1,2,3,4-tetrahydroquinoxaline (**1**) was extensively studied, for the 2-hydroxymethyl group of **1** would be an easy source of various functional groups on a reduced quinoxaline ring *via* routine oxidation, reduction, and displacement reactions.

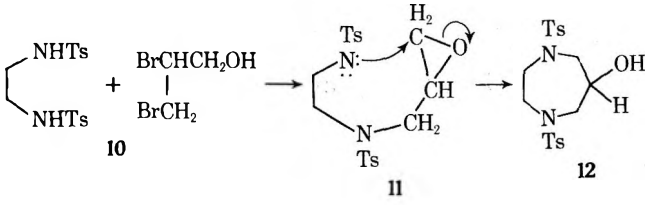
Condensation of the disodium salt of *N,N'*-bis(*p*-toluenesulfonyl)-o-phenylenediamine (**2**) with 2,3-dibromo-1-propanol (**3**) by the procedure of Acheson[4] gave ditosyl alcohol **4a**, mp 194–195°, reported[4] mp 193° for supposed 1,4-bis(*p*-toluenesulfonyl)-2-hydroxymethyl-1,2,3,4-tetrahydroquinoxaline (**1**). Detosylation of alcohol **4a** with sulfuric acid gave alcohol **5a**, mp 139–140°, reported[4] mp 140–141° for supposed 2-hydroxymethyl-1,2,3,4-tetrahydroquinoxaline (**6**). Oxidation of alcohol **5a** by a variety of agents was unsuccessful; however, oxidation of ditosyl alcohol **4a** with Jones reagent[5-7] gave a carbonyl compound (**7**), mp 179–180°, which readily formed an oxime, a hydrazone, a tosylhydrazone, and a 2,4-dinitrophenylhydrazone, and which was stable to Tollens and Benedict solutions. The nmr spectrum of **7** showed, in addition to the tosyl methyl and aromatic signals, only a sharp singlet at δ 4.06 for four protons, thus indicating a very symmetrical molecule, to which was assigned the structure 1,5-bis(*p*-toluenesulfonyl)-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-3-one (**7**). Mertes and Lin[3] have also reported this ketone. They concluded that alcohol **1** rearranged to ketone **7** during oxidation with dicyclohexylcarbodiimide in dimethyl sulfoxide. We conclude, however, that the reported[4] structure of **1** is incorrect and, in fact, is 1,5-bis(*p*-toluenesulfonyl)-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-3-ol (**4a**), and Acheson's detosylated alcohol is 2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-3-ol (**5a**), not 2-hydroxymethyl-1,2,3,4-tetrahydroquinoxaline (**6**) as reported.[4] The *O*-mesylate (**4b**) and *O*-tosylate (**4c**) derivatives of **4a** and the *N,N'*-diacetyl (**5b**) and *N,N'*-dinitroso (**5c**) derivatives of **5a** have also been prepared and have properties consistent with the benzodiazepine structure.

Sodium borohydride reduction of ketone **7** gave material identical (melting point, mixture melting point, ir) to diazepinol **4a**, thus ruling out formation of ketone **7** from alcohol **1** by rearrangement during oxidation. Retosylation of diazepinol **5a** with tosyl chloride in a variety of media (pyridine, aqueous potassium bicarbonate, or acetic acid–sodium acetate–tetrahydrofuran[8]) generally resulted in noncrystallizable oils. However, the oil from tosylation of **5a** in the acidic medium crystallized from ethanol after standing at 0° for several weeks to give a 6% yield of solid

Scheme I



Scheme II



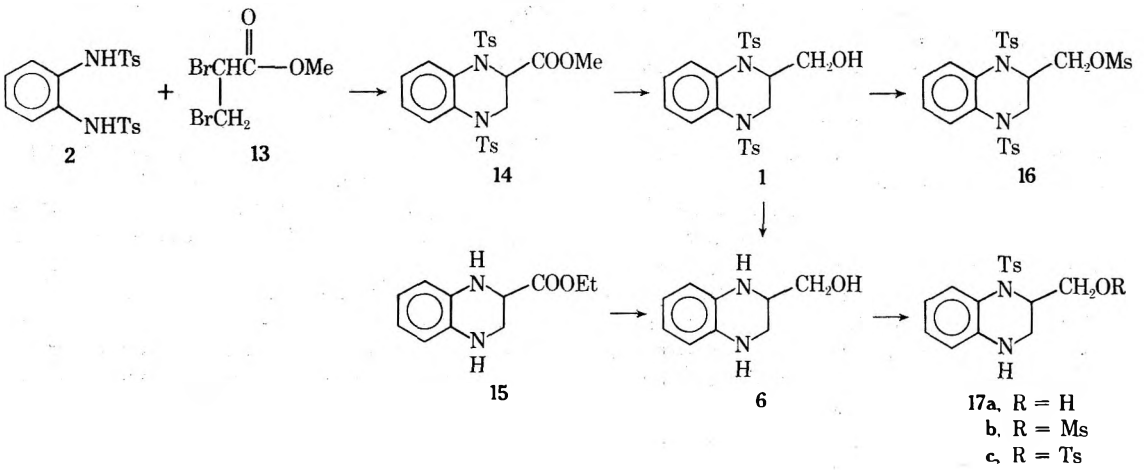
identical (melting point, mixture melting point, ir) to diazepinol **4a**, thus demonstrating that no rearrangement of diazepinol **4a** occurred during detosylation.

Diazepinol **4a** could also be formed by condensation of the disodium salt of **2** with epibromohydrin (**8**). Thus, formation of diazepinol **4a** from both 2,3-dibromo-1-propanol and epibromohydrin suggested the presence of a common intermediate such as epoxide **9** (Scheme I).[9] Ring opening of epoxide **9**, as shown, occurs at the preferred terminal methylene position to form the seven-membered diazepine ring system. Support for this conclusion was derived from a report by Saari, Raab, and King[10] that condensation of the disodium salt of *N,N'*-ethylenebis(*p*-toluenesulfonamide) (**10**) with 2,3-dibromo-1-propanol gave mainly 1,4-bis(*p*-toluenesulfonyl)-1*H*-1,4-diazepin-6-ol (**12**), presumably *via* the corresponding 1-N-substituted 2,3-epoxypropane (**11**) (Scheme II).

Additional evidence that alcohol **4a** was a secondary alcohol, and not the primary alcohol **1**, was shown by the appearance of the hydroxyl proton as a doublet (J = 4.5 Hz) at δ 5.41 when its nmr spectrum was recorded in DMSO-d_6.[11,12] Similarly, the nmr spectra in DMSO-d_6 of the detosylated alcohol **5a**, and its *N,N'*-diacetyl (**5b**) and *N,N'*-dinitroso (**5c**) derivatives showed doublets at δ 4.55 (J = 6 Hz), 5.43 (J = 5 Hz), and 5.54 (J = 3 Hz), respectively, for the hydroxyl protons. That these doublets were the result of the hydroxyl proton coupling with one neighboring proton was confirmed by their disappearance upon addition of D_2O to the nmr samples.

Authentic 1,4-bis(*p*-toluenesulfonyl)-2-hydroxymethyl-1,2,3,4-tetrahydroquinoxaline (**1**) was obtained by the sequence shown in Scheme III. Condensation of *N,N'*-bis(*p*-toluenesulfonyl)-*o*-phenylenediamine (**2**) with methyl 2,3-dibromopropionate[13] (**13**) in methanolic potash by the procedure of Negishi and Day[14] gave 1,4-bis(*p*-toluenesulfonyl)-2-carbomethoxy-1,2,3,4-tetrahydroquinoxaline (**14**), which was reduced with lithium aluminum hydride to give alcohol **1**, mp 134–135°. The physical and spectral properties of authentic **1** were completely different from those previously reported by Acheson[4] for his supposed **1**. Confirmation of the primary alcohol character of **1** was obtained by recording its nmr spectrum in DMSO-d_6, with the hydroxyl proton appearing as a triplet (J = 5.5 Hz) at δ 5.19, which disappeared upon addition of D_2O to the sample. Treatment of alcohol **1** with mesyl chloride in pyridine gave the *O*-mesylate derivative **16**, whose nmr

Scheme III



spectrum was consistent with the tetrahydroquinoxaline structure.

Detosylation of alcohol 1 with sulfuric acid gave a viscous, high-boiling, noncrystallizable, red oil, identical (ir) with 2-hydroxymethyl-1,2,3,4-tetrahydroquinoxaline (6), obtained by lithium aluminum hydride reduction of 2-carboethoxy-1,2,3,4-tetrahydroquinoxaline[15] (15). Alcohol 6 was analyzed as its *N*-tosyl derivative **17a**, to which has been assigned the structure 1-*p*-toluenesulfonyl-2-hydroxymethyl-1,2,3,4-tetrahydroquinoxaline.[16] The nmr spectrum of **17a** in DMSO-d_6 showed a triplet (J = 5.5 Hz) at δ 4.84 characteristic of a primary hydroxyl proton. The *O*-mesylate (**17b**) and *O*-tosylate (**17c**) derivatives also have properties that are consistent with the assigned 2-hydroxymethyltetrahydroquinoxaline structure.

Experimental Section[17]

***N,N'*-Bis(*p*-toluenesulfonyl)-*o*-phenylenediamine (2).** This was prepared in 93% yield from *o*-phenylenediamine and TsCl in C_5H_5N by the method of Acheson[4] and was recrystallized from EtOH (4 ml/g) to constant mp 205–207° (lit.[4] mp 204°, lit.[18] mp 203–202°).

1,5-Bis(*p*-toluenesulfonyl)-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-3-ol (4a). Condensation of the disodium salt of 2 with 2,3-dibromo-1-propanol (3) by the method of Acheson[4] gave **4a** in 41.2% yield, mp 194–195° (lit.[4] mp 193° for supposed alcohol 1), recrystallized from EtOH (7 ml/g). Alcohol **4a** was also obtained in 23% yield by the same procedure using epibromohydrin (8) in place of 2,3-dibromopropanol: ir (KBr) 3510 (OH), 1330, 1150 cm^{-1} (CSO_2); uv max 200 nm (end absorption), 230 (ϵ 26,800); nmr ($CDCl_3$) δ 2.40 (s, 6, $TsCH_3$), 3.05 (br s, 1, OH), 3.59 (m, 4, NCH_2), 3.80 (m, 1, CHO), 7.34 (m, 8, Ts aromatic), 7.83 (m, 4, benzo aromatic); nmr (DMSO-d_6) δ 5.41 (d, J = 4.5 Hz, 1, OH).

1,5-Bis(*p*-toluenesulfonyl)-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-3-ol Methanesulfonate (4b). To a cold (−5°) solution of 0.2 ml (0.3 g, 2.6 mmol) of MsCl in 2.0 ml of dry C_5H_5N was added dropwise over 0.25 hr a solution of 0.23 g (0.49 mmol) of alcohol **4a** in 2.0 ml of dry C_5H_5N. The solution was stirred at 0° for 3 hr, diluted with 25 ml of ice and H_2O, cooled, and filtered to give 0.20 g (74.2%) of white solid, mp 199–201°, which was recrystallized from $CHCl_3$–ligroin (15 ml/g, 2:1) to constant mp 203–204°: ir (KBr) 1350, 1165 cm^{-1} (CSO_2); uv max 200 nm (end absorption), 230 (ϵ 25,800); nmr ($CDCl_3$) δ 2.41 (s, 6, $TsCH_3$), 2.98 (s, 3, $MsCH_3$), 3.1–3.5, 3.9–4.3 (m, 4, NCH_2), 4.5–5.0 (m, 1, CHO), 7.35 (m, 8, Ts aromatic), 7.85 (m, 4, benzo aromatic).

Anal. Calcd for $C_{24}H_{26}N_2O_7S_3$: C, 52.34; H, 4.76; N, 5.09. Found: C, 52.02; H, 4.75; N, 4.98.

1,5-Bis(*p*-toluenesulfonyl)-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-3-ol *p*-Toluenesulfonate (4c). A solution of 0.95 g (2.0 mmol) of alcohol **4a** and 0.76 g (4.0 mmol) of TsCl in 2.5 ml of dry C_5H_5N was refluxed for 1 hr. The solution was cooled, poured onto 5 ml of ice and H_2O, and filtered to give 1.22 g (97.6%) of white solid, mp 187–189°, which was recrystallized from $CHCl_3$–ligroin (5 ml/g, 2:1) to constant mp 192–193° (lit.[3] mp 186–188°): ir (KBr) 1357, 1167 cm^{-1} (CSO_2); uv max 200 nm (end absorption), 228 (ϵ 40,900); nmr ($CDCl_3$) δ 2.41 (s, 6, $NTsCH_3$), 2.50 (s, 3, $OTsCH_3$), 2.6–3.1, 3.9–4.3 (m, 4, NCH_2), 4.3–4.7 (m, 1, CHO), 7.2–8.0 (m, 16, aromatic).

Anal. Calcd for $C_{30}H_{30}N_2O_7S_3$: C, 57.49; H, 4.82; N, 4.47. Found: C, 57.62; H, 4.82; N, 4.51.

2,3,4,5-Tetrahydro-1*H*-1,5-benzodiazepin-3-ol (5a). Alcohol **4a** was detosylated by standing in concentrated H_2SO_4 (10 ml/g) for 48 hr at room temperature and was worked up according to the method of Acheson[4] to give **5a** in 81% yield, which was recrystallized from EtOH (7 ml/g) to constant mp 139–140° (lit.[4] mp 140–141° for supposed alcohol 6): ir (KBr) 3380, 3290 (NH), 3100–3400 cm^{-1} (br, OH); uv max 218 nm (ϵ 25,200), 248 sh (4140), 296 (2300); nmr ($CDCl_3$) δ 2.90 (2 d, J_{vic} = 2 Hz, J_{gem} = −12 Hz, 2 NCH_2 ax), 3.30 (2 d, J_{vic} = 5 Hz, J_{gem} = −12 Hz, 2, NCH_2 eq), 3.57 (s, 3, NH's and OH), 3.83 (m, 1, CHO), 6.77 (s, 4, aromatic): nmr (DMSO-d_6) δ 4.55 (d, J = 6 Hz, 1, OH), 4.85 (br s, 2, NH's).

Retosylation of Alcohol 5a. A cold (5°) solution of 0.16 g (1.0 mmol) of alcohol **5a**, 1.5 ml of H_2O, 0.2 ml of glacial HOAc, 0.4 ml of THF, and 0.21 g (1.1 mmol) of TsCl was stirred for 15 hr while warming up to room temperature. The solution was diluted with 15 ml of H_2O and extracted with $CHCl_3$. The extracts were dried ($MgSO_4$), treated with Norit and Celite, and evaporated under vacuum (30°) to give 0.16 g (34.1%) of tan oil. The oil was dissolved in 3 ml of hot EtOH, treated with Norit and Celite, and kept at 0° for about 1 month, after which it partially crystallized. Filtration of the solution gave 0.003 g (6.4%) of tan solid, mp 187–190°, mmp with **4a** 188–191°, mmp with **4c** 165–168° (**4a** and **4c** mmp 170–174°).

1,5-Diacetyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-3-ol (5b). A solution of 0.82 g (5.0 mmol) of alcohol **5a** in 5.0 ml of Ac_2O was allowed to stand at room temperature for 1.5 hr. The precipitated solid was filtered and washed with H_2O to give 1.16 g (93.5%) of white solid, mp 219–221°, which was recrystallized from EtOH (10 ml/g) to constant mp 222–223°: ir (KBr) 3420 (OH), 1650 cm^{-1} (C=O); uv max 200 nm (end absorption), 217 (ϵ 16,200), 262 (1680); nmr (DMSO-d_6) δ 1.79 (s, 6, $COCH_3$), 2.23, 4.66 (m, 4, NCH_2), 3.65 (m, 1, CHO), 5.43 (d, J = 5 Hz, 1, OH), 7.57 (s, 4, aromatic).

Anal. Calcd for $C_{13}H_{16}N_2O_3$: C, 62.89; H, 6.50; N, 11.28. Found: C, 62.63; H, 6.33; N, 11.24.

1,5-Dinitroso-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-3-ol (5c). To a solution of 0.82 g (5.0 mmol) of alcohol **5a**, 5 ml of H_2O, and 1 ml of 12 *N* HCl, cooled to 5° in an ice bath, was added dropwise with stirring over 0.5 hr a cold (10°) solution of 0.76 g (11.0 mmol) of $NaNO_2$ in 5 ml of H_2O. The solution was stirred until precipitation had occurred (0.5–2 hr) to give 1.03 g (92.8%) of tan solid, mp 122–124°, which was recrystallized from C_6H_6 (30 ml/g) to constant mp 126–127°: ir (KBr) 3340 (OH), 1450 cm^{-1} (NNO); uv max 217 (ϵ 7430), 271 (15,100), 380 (667); nmr (DMSO-d_6) δ 4.02 (br, s, 4, NCH_2), 4.3–4.7 (m, 1, CHO), 5.54 (d, J = 3 Hz, 1, OH), 7.2–8.0 (m, 4, aromatic).

Anal. Calcd for $C_9H_{10}N_4O_3$: C, 48.65; H, 4.54; N, 25.21. Found: C, 48.42; H, 4.35; N, 25.25.

1,5-Bis(*p*-toluenesulfonyl)-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepin-3-one (7). A mixture of 4.73 g (10.0 mmol) of alcohol **4a**, 50 ml of acetone, and 6.0 ml of Jones reagent[5-7] (2.67 g of CrO_3 dissolved in 2.3 ml of concentrated H_2SO_4 diluted to 10 ml with H_2O) was refluxed with stirring for 6 hr. After cooling, the solution was decanted from the inorganic salts, concentrated under vacuum (30°) to 10 ml, diluted with 20 ml of H_2O, cooled, and filtered to give 4.20 g (89.4%) of white solid, mp 170–175°. The product was recrystallized from $CHCl_3$–EtOH (12 ml/g, 1:1) to yield 3.24 g (68.9%) of white solid: mp 179–180° (lit.[3] mp 176–178°); ir (KBr) 1755 (C=O), 1350, 1155 cm^{-1} (CSO_2); uv max 200 nm (end absorption), 229 (ϵ 32,200); nmr ($CDCl_3$) δ 2.40 (s, 6, $TsCH_3$), 4.06 (s, 4, NCH_2), 7.1–7.7 (m, 12, aromatic).

Anal. Calcd for $C_{23}H_{22}N_2O_5S_2$: C, 58.71; H, 4.71; N, 5.95. Found: C, 58.87; H, 4.76; N, 6.00.

Derivatives of Ketone 7. Oxime: white solid, mp 198–198.5°, recrystallized from EtOH–H_2O (30 ml/g, 5:1). *Anal.* Calcd for $C_{23}H_{23}N_3O_5S_2$: C, 56.89; H, 4.77; N, 8.56. Found: C, 56.88; H, 4.81; N, 8.60.

Hydrazone: white solid, mp 184–185°, recrystallized from EtOH–$CHCl_3$ (20 ml/g, 2:1). *Anal.* Calcd for $C_{23}H_{24}N_4O_4S_2$: C, 57.01; H, 4.99; N, 11.56. Found: C, 57.07; H, 4.99; N, 11.57.

Tosylhydrazone: white solid, mp 187–188°, recrystallized from EtOH (50 ml/g). *Anal.* Calcd for $C_{30}H_{30}N_4O_6S_3$: C, 56.41; H, 4.73; N, 8.77. Found: C, 56.16; H, 4.65; N, 8.71.

2,4-Dinitrophenylhydrazone: yellow solid, mp 200–201°, recrystallized from $CHCl_3$–EtOH (100 ml/g, 1:4). *Anal.* Calcd for $C_{29}H_{26}N_6O_8S_2$: C, 53.53; H, 4.03; N, 12.92. Found: C, 53.28; H, 3.94; N, 12.74.

$NaBH_4$ Reduction of Ketone 7. A mixture of 0.47 g (1.0 mmol) of ketone 7 and 0.19 g (5.0 mmol) of $NaBH_4$ in 10 ml of THF was refluxed with stirring for 3.5 hr. After cooling, 1.25 ml of H_2O and 5 drops of 6 *N* NaOH were added, and the solution was stirred for 0.5 hr. The layers were separated; the organic layer was dried ($MgSO_4$), treated with Norit and Celite, and evaporated under vacuum (30°) to give a viscous, yellow oil, which crystallized upon addition of 5 ml of EtOH to yield 0.43 g (91.2%) of white solid, mp 193–194°, identical with diazepinol **4a**, mmp 193–194°.

1,4-Bis(*p*-toluenesulfonyl)-2-carbomethoxy-1,2,3,4-tetrahydroquinoxaline (14). To 4.49 g (0.08 mol) of KOH dissolved in 50 ml of MeOH was added 16.6 g (0.04 mol) of *N,N'*-bis(*p*-toluenesulfonyl)-o-phenylenediamine (2), which immediately dissolved and then precipitated out as its potassium salt. Methyl 2,3-dibromopropionate (9.84 g, 0.04 mol, 5.3 ml) was added dropwise over 0.25 hr, and the resulting mixture was refluxed with stirring for 22 hr. After cooling, the solution was filtered, and the collected solid was triturated with 100 ml of H_2O and refiltered to give 15.1 g (75.5%) of white solid, mp 138–142°. The solid was recrystallized

from MeOH (25 ml/g) to give 3.33 g of unreacted diamine 2 and 10.7 g (53.5%) of white solid, mp 140–148°. Two recrystallizations from acetone (2 ml/g) gave 7.84 g (39.2%) of white solid of constant mp 144–145°: ir (KBr) 1735 (C=O), 1350, 1165 cm^{-1} (CSO_2); uv max 216 nm (ϵ 28,000), 224 sh (27,800); nmr ($CDCl_3$) δ 2.37 (s, 6, $TsCH_3$), 3.68 (s, 3, OCH_3), 3.75 (2 d, J_{vic} = 6 Hz, J_{gem} = −13 Hz, 1, NCH_2 ax), 4.17 (2 d, J_{vic} = 6 Hz, J_{gem} = −13 Hz, 1, NCH_2 eq), 5.21 (t, J = 6 Hz, 1, NCH), 6.95–7.85 (m, 12, aromatic).

Anal. Calcd for $C_{24}H_{24}N_2O_6S_2$: C, 57.58; H, 4.83; N, 5.60. Found: C, 57.34; H, 4.67; N, 5.47.

1,4-Bis(*p*-toluenesulfonyl)-2-hydroxymethyl-1,2,3,4-tetrahydroquinoxaline (1). A solution of 1.0 g (2.0 mmol) of ester **14** in 9 ml of dry THF was added dropwise over 1 hr to a stirred suspension of 0.50 g (13.0 mmol) of $LiAlH_4$ in 15 ml of dry THF. The mixture was stirred at room temperature for 1 hr and cooled in an ice bath; the excess of $LiAlH_4$ was destroyed by successive, dropwise addition of 0.5 ml of H_2O, 0.4 ml of 20% NaOH, and 2.5 ml of H_2O, followed by 20 ml of $CHCl_3$ to extract the organic product. After refluxing with stirring for 1 hr more, the solution was filtered. The filtrate was dried ($MgSO_4$), treated with Norit and Celite, and evaporated under vacuum (30°) to give 0.90 g (95.3%) of yellow oil. The oil was dissolved in $CHCl_3$ (4 ml) and passed through a 1-ft Florisil column eluted with $CHCl_3$ (75 ml). Evaporation of the eluent gave 0.88 g (93.2%) of viscous, yellow oil, which crystallized upon seeding and standing overnight at room temperature to give 0.46 g (48.8%) of white solid, mp 131–136°. Recrystallization from EtOH (5 ml/g) gave a white solid of constant mp 134–135°: ir (KBr) 3480 (OH), 1346, 1157 cm^{-1} (CSO_2); uv max 214 nm (ϵ 36,200), 260 sh (13,100); nmr (DMSO-d_6) δ 2.37 (s, 6, $TsCH_3$), 3.30 (m, 2, NCH_2), 4.08 (m, 2, CH_2O), 4.50 (m, 1, NCH), 5.19 (t, J = 5.5 Hz, 1, OH), 6.9–7.8 (m, 12, aromatic).

Anal. Calcd for $C_{23}H_{24}N_2O_5S_2$: C, 58.46; H, 5.12; N, 5.93. Found: C, 58.24; H, 5.07; N, 5.91.

1,4-Bis(*p*-toluenesulfonyl)-2-hydroxymethyl-1,2,3,4-tetrahydroquinoxaline Methanesulfonate (16). To 0.50 g (1.06 mmol) of alcohol **1** in 5.0 ml of dry C_5H_5N cooled at 5° was added 0.5 ml (0.75 g, 6.5 mmol) of MsCl. The solution was stirred for 3 hr, poured onto 20 ml of ice and H_2O, and filtered to give 0.55 g (94.2%) of white solid, mp 123–125°. Recrystallization from EtOH (20 ml/g) gave solid of constant mp 138.5–139.5°. Recrystallization from $CHCl_3$–ligroin (6 ml/g, 1:1) gave a mixture of this high-melting solid and a lower melting white powder, mp 128–129°. The ir and nmr spectra of these solids were identical, and both gave satisfactory elemental analyses, thus indicating different crystal structures of the same compound. Recrystallization of the lower melting solid from EtOH raised its melting point to that of the higher melting solid: ir (KBr) 1350, 1163 cm^{-1} (CSO_2); uv max, 200 nm (end absorption), 216 (ϵ 36,200), 232 sh (33,500); nmr ($CDCl_3$) δ 2.39 (s, 6, $TsCH_3$), 3.03 (s, 3, $MsCH_3$), 3.67 (t, J = 6 Hz, 2, NCH_2), 4.23 (m, 2, CH_2O), 4.77 (m, 1, NCH), 6.9–7.9 (m, 12, aromatic).

Anal. Calcd for $C_{24}H_{26}N_2O_7S_3$: C, 52.35; H, 4.76; N, 5.09. Found (mp 128–129°): C, 52.49; H, 4.68; N, 5.05. Found (mp 138.5–139.5°): C, 52.36; H, 4.76; N, 5.06.

2-Hydroxymethyl-1,2,3,4-tetrahydroquinoxaline (6). A. By Detosylation of 1. A mixture of 0.47 g (1.0 mmol) of alcohol **1** and 5 ml of concentrated H_2SO_4 was allowed to stand at room temperature for 24 hr. The solution was diluted with 30 ml of ice-water, basified to pH 10 with 30 ml of concentrated NH_4OH, and extracted with $CHCl_3$. The extracts were dried ($MgSO_4$), treated with Norit and Celite, and evaporated under vacuum (30°) to give 0.08 g (48.7%) of viscous, yellow oil, identical by ir with **6** prepared by method B.

B. By Reduction of Ester 15. A solution of 3.09 g (15.0 mmol) of 2-carboethoxy-1,2,3,4-tetrahydroquinoxaline[15] (**15**) in 50 ml of dry Et_2O was added dropwise over 1 hr to a stirred suspension of 2.28 g (60.0 mmol) of $LiAlH_4$ in 30 ml of dry Et_2O. The mixture was refluxed for 1 hr and cooled in an ice bath; the excess $LiAlH_4$ was destroyed by successive, dropwise addition of 2.3 ml of H_2O, 1.7 ml of 20% NaOH, and 8.0 ml of H_2O, followed by 50 ml of $CHCl_3$ to extract the organic product. After refluxing for 1 hr with stirring, the solution was filtered. The filtrate was dried ($MgSO_4$), treated with Norit and Celite, and evaporated under vacuum (30°) to give 2.34 g (95.2%) of viscous, yellow oil, identical by ir with **6** prepared by method A. Vacuum distillation of the oil gave 1.85 g (75.3%) of viscous, red oil: bp 175–180° (1 mm) (all attempts to crystallize the oil failed); ir (neat) 3430 cm^{-1} (OH); uv max 218 nm (ϵ 34,500), 256 (5200), 311 (4340); nmr ($CDCl_3$) δ 3.15 (m, 2, NCH_2), 3.34 (m, 1, NCH), 3.50 (br s, 2, CH_2O), 3.52 (s, 3, NH's and OH), 6.56 (m, 4, aromatic).

1-*p*-Toluenesulfonyl-2-hydroxymethyl-1,2,3,4-tetrahydroquinoxaline (17a). A mixture of 1.34 g (8.2 mmol) of alcohol **6**, 1.0 g (10.0 mmol) of $KHCO_3$, 2.0 g (10.4 mmol) of TsCl, 5 ml of THF, and 5 ml of H_2O was stirred at room temperature for 3 hr. The THF was evaporated under vacuum (30°) and the H_2O was decanted off, leaving an oily residue which was triturated with two 20-ml portions of hot ligroin (bp 63–75°) to remove unreacted TsCl. The residue remaining crystallized to give 2.12 g (81.6%) of tan solid, mp 135–144°. Two recrystallizations from EtOH (5 ml/g) gave 1.43 g (55.0%) of white solid: mp 147.5–148.5°; ir (KBr) 3510 (OH), 3330 (NH), 1335, 1156 cm^{-1} (CSO_2); uv max 215 nm (ϵ 30,800), 243 (18,300), 307 (4920); nmr ($CDCl_3$) δ 2.35 (s, 3, $TsCH_3$), 3.26 (m, 2, NCH_2), 3.47 (m, 2, CH_2O), 4.11 (m, 1, NCH), 2.9–3.6 (br m, 2, NH and OH), 6.4–7.7 (m, 8, aromatic); nmr (DMSO-d_6) δ 4.84 (t, J = 5.5 Hz, 1, OH), 5.88 (br s, 1, NH).

Anal. Calcd for $C_{16}H_{18}N_2O_3S$: C, 60.36; H, 5.70; N, 8.80. Found: C, 60.16; H, 5.64; N, 8.69.

1-*p*-Toluenesulfonyl-2-hydroxymethyl-1,2,3,4-tetrahydroquinoxaline Methanesulfonate (17b). To a stirred, cold (−5°) solution of 2.0 ml (3 g, 26 mmol) of MsCl in 5 ml of dry C_5H_5N was added dropwise over 0.5 hr a solution of 3.18 g (10.0 mmol) of alcohol **17a** in 10.0 ml of dry C_5H_5N. The solution was stirred at 0° for 3 hr, poured onto 100 ml of ice and H_2O, cooled, and filtered to give 3.92 g (99%) of off-white solid, mp 148–151°. Recrystallization from $CHCl_3$–ligroin (20 ml/g, 2:1) gave a white solid of constant mp 154–155°: ir (KBr) 3390 (NH), 1345, 1170 cm^{-1} (CSO_2); uv max 200 nm (end absorption), 214 (ϵ 34,700), 237 (16,800), 308 (3660); nmr ($CDCl_3$) δ 2.36 (s, 3, $TsCH_3$), 3.50 (s, 3, $MsCH_3$), 3.92 (m, 2, NCH_2), 4.02 (m, 3, CH_2O and NCH), 4.14 (br s, 1, NH), 6.4–7.7 (m, 8, aromatic).

Anal. Calcd for $C_{17}H_{20}N_2O_5S_2$: C, 51.50; H, 5.08; N, 7.07. Found: C, 51.69; H, 5.25; N, 7.07.

1-*p*-Toluenesulfonyl-2-hydroxymethyl-1,2,3,4-tetrahydroquinoxaline *p*-Toluenesulfonate (17c). To 0.32 g (1.0 mmol) of alcohol **17a** in 4.0 ml of dry C_5H_5N cooled to 5° was added 0.38 g (2.0 mmol) of TsCl. The solution was kept at 0° for 5 days, then diluted with 20 ml of ice–water, acidified with 6 *N* HCl, and extracted with $CHCl_3$. The extracts were dried ($MgSO_4$), treated with Norit and Celite, concentrated to 5 ml, and diluted with 5 ml of ligroin to give 0.32 g (66.7%) of light yellow solid, mp 127–130°. Recrystallization from $CHCl_3$–ligroin (10 ml/g, 1:1) gave a white solid of constant mp 131–132°. The product was unstable, turning purple-gray upon prolonged standing, and many times it was never formed by the above procedure: ir (KBr) 3390 (NH), 1350, 1162 cm^{-1} (CSO_2); uv max 200 nm (end absorption), 216 (ϵ, 37,000), 244 sh (14,200), 309 (2130); nmr ($CDCl_3$) δ 2.34 (s, 3, $NTsCH_3$), 2.42 (s, 3, $OTsCH_3$), 3.20 (m, 2, NCH_2), 3.98 (m, 3, CH_2O and NCH), 4.79 (br s, 1, NH), 6.35–7.85 (m, 12, aromatic).

Anal. Calcd for $C_{23}H_{24}N_2O_5S_2$: C, 58.46; H, 5.12; N, 5.93. Found: C, 57.85; H, 5.07; N, 5.63.

Registry No. **1**, 49633-27-4; **2**, 49633-28-5; **3**, 96-13-9; **4a**, 49633-29-6; **4b**, 49633-30-9; **4c**, 49633-31-0; **5a**, 49633-32-1; **5b**, 49633-33-2; **5c**, 49633-34-3; **6**, 49633-35-4; **7**, 1179-18-6; **7** oxime, 49633-37-6; **7** hydrazone, 49633-38-7; **7** tosylhydrazone, 49633-39-8; **7** 2,4-dinitrophenylhydrazone, 1183-85-3; **8**, 3132-64-7; **14**, 49633-41-2; **15**, 49633-42-3; **16**, 49633-43-4; **17a**, 49633-44-5; **17b**, 49633-45-6; **17c**, 49689-60-3.

References and Notes

(1) (a) Part XX of this series: H. R. Moreno, J. E. Oatis, Jr., and H. P. Schultz, *J. Med. Chem.*, **15**, 433 (1972); (b) NSF Trainee 1969–1972; abstracted from the Ph.D. dissertation of G. H. F.

(2) S. J. Benkovic, P. A. Benkovic, and D. R. Comfort, *J. Amer. Chem. Soc.*, **91**, 5270 (1969); S. J. Benkovic, P. A. Benkovic, and R. Chrzanowski, *ibid.*, **92**, 523 (1970); S. J. Benkovic, W. P. Bullard, and P. A. Benkovic, *ibid.*, **94**, 7542 (1972).

(3) M. P. Mertes and A. J. Lin, *J. Med. Chem.*, **13**, 77 (1970).

(4) R. M. Acheson, *J. Chem. Soc.*, 4731 (1956).

(5) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).

(6) A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *J. Chem. Soc.*, 2548 (1953).

(7) C. Djerassi, R. R. Engle, and A. Bowers, *J. Org. Chem.*, **21**, 1547 (1956).

(8) G. H. Fisher and H. P. Schultz, *J. Org. Chem.*, **39**, 635 (1974).

(9) Rearrangement of 2,3-dibromo-1-propanol to 1,3-disubstituted 2-propanol derivatives *via* epoxide intermediates has been proposed by W. W. Paudler, G. R. Gapski, and J. M. Barton, *J. Org. Chem.*, **31**, 277 (1966); F. P. Doyle and J. H. C. Nayler, *Chem. Ind. (London)*, 714 (1955); and F. C. Whitmore, H. S. Mosher, D. P. Spalding, R. B. Taylor, G. W. Moersch, and W. H. Yanko, *J. Amer. Chem. Soc.*, **68**, 531 (1946).

(10) W. S. Saari, A. W. Raab, and S. W. King, *J. Org. Chem.*, **36**, 1711 (1971).
(11) O. L. Chapman and R. W. King, *J. Amer. Chem. Soc.*, **86**, 1256 (1964).
(12) J. G. Traynham and G. A. Knesel, *ibid.*, **87**, 4220 (1965).
(13) G. Münder and B. Tollens, *Justus Liebigs Ann. Chem.*, **167**, 222 (1873).
(14) E. Negishi and A. R. Day, *J. Org. Chem.*, **30**, 43 (1965).
(15) G. F. Bettinetti, *Ann. Chim. (Rome)*, **51**, 920 (1961; *Chem. Abstr.*, **57**, 5914c (1962).
(16) Proof of the structure of the *N*-tosyl derivative **17a** is presented in the following paper (ref 8).
(17) Melting points, uncorrected, were determined on a Thomas-Hoover apparatus. Spectra were recorded as follows: uv, Jasco ORD/UV-5 in 95% ethanol in 1-cm quartz cells; H nmr, Hitachi Perkin-Elmer R-20, 60 MHz, 34° in δ, parts per million from internal TMS; ir, Beckman IR-10. Elemental analyses were performed by PCR, Inc., Gainesville, Fla. Ligroin was medium boiling, bp 66–75°. THF and C_5H_5N were dried over CaH_2 and redistilled.
(18) F. Reverdin and P. Crepieux, *Ber.*, **35**, 314 (1902).

Quinoxaline Studies. XXII.[1a] Tosylation and Chiralities of 2-Substituted 1,2,3,4-Tetrahydroquinoxalines

George H. Fisher[1b] and Harry P. Schultz*

Department of Chemistry, University of Miami, Coral Gables, Florida 33124

Received August 2, 1973

Tosylation of several 2-substituted 1,2,3,4-tetrahydroquinoxalines (methyl, hydroxymethyl, carboxamide, carboxylic acid, or carboethoxy) gave exclusively *N*-monotosyl derivatives whose nmr spectra justified assignment of the tosyl group to the 1-N position. Support for this assignment was obtained by comparing the nmr spectra of unsubstituted and N-tosylated tetrahydroquinolines and tetrahydroquinaldines as model compounds. The tosyl derivatives were then utilized to establish the C-2 chiralities of the various 2-substituted 1,2,3,4-tetrahydroquinoxalines according to the sequence (*RS*)-1,2,3,4-tetrahydroquinoxaline-2-carboxamide, (*R*)-1,2,3,4-tetrahydroquinoxaline-2-carboxamide, (*R*)-1-*p*-toluenesulfonyl-1,2,3,4-tetrahydroquinoxaline-2-carboxamide, (*R*)-1-*p*-toluenesulfonyl-1,2,3,4-tetrahydroquinoxaline-2-carboxylic acid, (*R*)-1-*p*-toluenesulfonyl-1,2,3,4-tetrahydro-2-hydroxymethylquinoxaline, and (*S*)-1-*p*-toluenesulfonyl-2-methyl-1,2,3,4-tetrahydroquinoxaline—the latter identical with the configurational standard prepared unequivocally from L-α-alanine.

Substituted tetrahydroquinoxalines are of interest as models for tetrahydrofolic acid.[2,3] It is the purpose of this paper to report that tosylation of the tetrahydroquinoxalines **1a–e** gave exclusively the 1-*N*-monotosyl derivatives **2a–e**, to present evidence in support of said structures, and to outline the utility of the above tosyl derivatives for establishing the chiralities of their various asymmetric centers, as well as of the asymmetric centers of the parent tetrahydroquinoxalines. Scheme I depicts the structures of the compounds prepared and utilized for this study.

Tosylation was carried out with tosyl chloride in the usual basic media of pyridine or aqueous sodium bicarbonate, or in the more unusual acidic medium of aqueous acetic acid–sodium acetate–tetrahydrofuran. In general, the acidic medium gave higher yields of purer product than the basic media, and reaction in acid favored N-tosylation *vs.* O-tosylation in case of **1e**. The single exception was tetrahydroquinoxaline-2-carboxylic acid (**1c**). In pyridine **1c** gave a mixture of the *N*-tosyl acid **2c** and the *N*-tosyl lactam **3**, identified by ir, nmr, and elemental analysis. Hydrolysis of lactam **3** in aqueous sodium hydroxide gave the *N*-tosyl acid **2c**. Tosylation of the acid **1c** in aqueous sodium bicarbonate gave small yields of the *N*-tosyl acid **2c**, while tosylation in acidic medium gave **2c** in good yield.

H-nmr evidence indicated that tosylation occurred at the 1-N position, contrary to N-acylation of 2-substituted tetrahydroquinoxalines, *e.g.*, monobenzoylation of 2-methyl- and 2-*tert*-butyl-1,2,3,4-tetrahydroquinoxaline which has been reported[4] to occur at the 4-N position.

The chemical shifts of the protons on the C-2 and C-3 atoms adjacent to the nitrogen atoms in tetrahydroquinoxalines are dependent on the diamagnetic anisotropy of nearby bonds or rings and the inductive effects of neighboring groups or atoms.[5] Since the tosyl group is electron withdrawing, its substitution on the 1-nitrogen predicates a greater downfield chemical shift difference for the C-2 methine proton than for the C-3 methylene protons when comparing the nmr spectra of the unsubstituted and the *N*-monotosyl tetrahydroquinoxalines. Table I demonstrates that all of the compounds studied showed such a chemical shift difference, thus warranting assignment of the tosyl group to the 1-N position in compounds **2a–e**.

In support of this assignment, the nmr spectra of the model compounds tetrahydroquinoline (**4a**), tetrahydroquinaldine (**4b**), and their N-tosyl derivatives **5a**[6] and **5b** showed (Table II) that a greater chemical shift difference was observed for the C-2 ring protons adjacent to the tosylated nitrogen than for the C-3 protons two carbon atoms removed from the substituted nitrogen. Similar shift effects have been observed[7,8] for *N*-acetyl-, *N*-benzoyl-, and *N*-thioacetyltetrahydroquinolines and -tetrahydroquinaldines.

The fact that tosylation of 2-substituted tetrahydroquinoxalines **1a–e** gave only the monotosyl derivatives **2a–e**, especially in the acidic medium (pH 4), was curious in light of a report by Morley[9] that acylation of tetrahydroquinoxaline gave predominantly 1,4-diacyl derivatives at pH <5, and monoacyl derivatives at a higher pH. Cavagnol and Wiselogle[10] reported that benzenesulfonation of tetrahydroquinoxaline in aqueous sodium hydroxide gave only the mono-*N*-benzenesulfonyl derivative. Also curious is the fact that tosylation of 2-methyltetrahydroquinoxaline (**1a**) gave the 1-*N*-tosyl derivative, whereas its reported acetylation or benzoylation gave first the 4-N-substituted derivative **6a,b** and then the 1,4-disubstituted derivative **7a,b**.[4] From the chemical shift data (Table III) for the mono (**6a,b**) and di (**7a,b**) derivatives it is seen that the monoacyl substituent causes a larger chemical shift difference for the C-3 equatorial proton when compared with the unsubstituted parent (**1a**), thus indicating that, in contrast to tosylation, the first acyl group goes to the 4-N position of the heteroring. Only on disubstitution is a significant shift of the C-2 proton observed, indicating the second acyl group to be in the 1-N position.

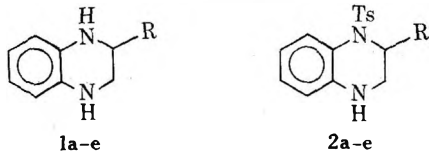
The divergence of results for tosylation *vs.* acylation of tetrahydroquinoxalines suggests that these reactions proceed by different mechanisms with the position of substitu-

Table I
Chemical Shifts and Shift Differences of 2-Substituted Tetrahydroquinoxalines and Their *N*-Tosyl Derivatives

Compd[a]	Solvent[b]	C-3 protons δ_{ax}[c]	C-3 protons $\Delta\delta$[d]	C-3 protons δ_{eq}	C-3 protons $\Delta\delta$	C-2 proton δ	C-2 proton $\Delta\delta$
1-Ts-2-Me-THQx	$CDCl_3$	2.78	−0.14	2.91	−0.35	4.15	0.73
2-Me-THQx	$CDCl_3$	2.92		3.26		3.42	
1-Ts-2-$CONH_2$-THQx	DMSO-d_6	3.32	0.10	3.32	0.10	4.26	0.49
2-$CONH_2$-THQx	DMSO-d_6	3.22		3.22		3.77	
1-Ts-2-COOH-THQx	DMSO-d_6	3.44	0.12	3.44	0.12	4.18	0.22
2-COOH-THQx	DMSO-d_6	3.32		3.32		3.96	
1-Ts-2-COOEt-THQx	$CDCl_3$	3.04	−0.29	3.44	−0.14	4.58	0.57
2-COOEt-THQx	$CDCl_3$	3.33		3.58		4.01	
1-Ts-2-CH_2OH-THQx	$CDCl_3$	3.26	0.11	3.26	0.11	4.11	0.77
2-CH_2OH-THQx	*$CDCl_3$*	*3.15*		*3.15*		*3.34*	

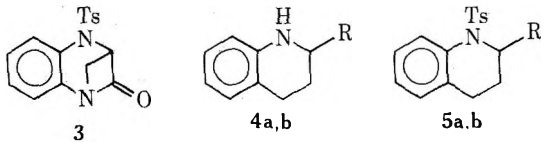
[a] THQx = tetrahydroquinoxaline. [b] Solutions were ~10% in the given solvent. [c] δ is in ppm from internal TMS. [d] $-\Delta\delta$ represents an upfield shift.

Scheme I



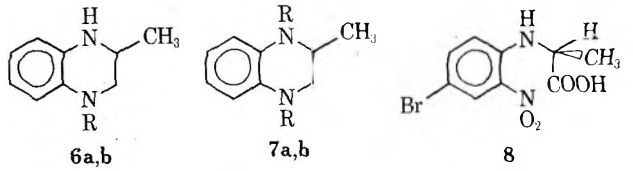
1a–e 2a–e

a, R = CH_3
b, R = $CONH_2$
c, R = *COOH*
d, R = $COOCH_2CH_3$
e, R = CH_2OH



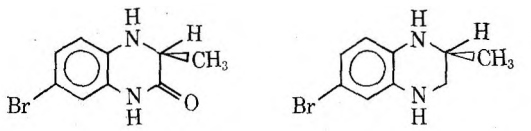
3 4a,b 5a,b

a, R = H
b, R = CH_3

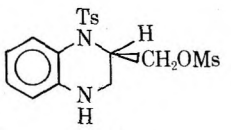


6a,b 7a,b 8

a, R = $COCH_3$
b, R = COC_6H_5



9 10



11

tion being controlled by different factors. It appears that acylation proceeds through an intermediate *via* an SN2-type mechanism[11] and is controlled by steric factors in which the bulk of the incoming acyl group causes substitution to occur at the least hindered 4-N position farthest away from the 2-alkyl group. Tosylation, however, appears to be controlled by electronic effects, such as increased basicity of the 1-nitrogen, which directs the incoming tosyl group to the 1-N position.

Archer and Mosher[12] have shown that 2-substituted tetrahydroquinoxalines exist predominantly in a half-chair conformation with the 2-alkyl group preferentially equatorial, as evidenced by a chemical shift difference of ~1 ppm downfield between the axial and the equatorial C-3 methylene protons. The extent to which the 1-nitrogen is coplanar with the aromatic ring is in doubt, based on a recent microwave determination which showed that the NH_2 group of aniline is not coplanar with the benzene ring.[13] Therefore, it is conceivable that the 2 substituent of 2-substituted tetrahydroquinoxalines, in seeking the equatorial position, forces the 1-nitrogen to be noncoplanar with the aromatic ring, thereby sterically inhibiting delocalization of the lone electron pair of the 1-nitrogen atom into the aromatic ring, increasing its basicity. Thus, the increased basicity of the 1-nitrogen over that of the 4-nitrogen atom attracts the incoming tosyl group to the 1-N position. The exact mechanism of N-tosylation and the reason why 2-substituted tetrahydroquinoxalines give only monotosyl derivatives are still unknown. Further investigation in these areas is warranted.

Table II
Chemical Shifts and Shift Differences of Tetrahydroquinolines and Their *N*-Tosyl Derivatives

Compd[a]	C-3 protons δ[b]	C-3 protons $\Delta\delta$[c]	C-2 proton(s) δ	C-2 proton(s) $\Delta\delta$
Ts-THQn	1.62	−0.26	3.78	0.55
THQn	1.88		3.23	
Ts-2-Me-THQn	1.72	−0.06	4.38	1.06
2-Me-THQn	1.78		3.32	

[a] THQn = tetrahydroquinoline. [b] δ is in ppm from internal TMS for ~10% solutions in $CDCl_3$. [c] $-\Delta\delta$ represents an upfield shift.

The structures of the various 1-tosyl-2-substituted 1,2,3,4-tetrahydroquinoxalines having been established, determinations of the chiralities of their asymmetric centers followed.

The unequivocal synthesis of (*S*)-2-methyl-1,2,3,4-tetrahydroquinoxaline [(*S*)-**1a**] from L-α-alanine and 2,4-dibromonitrobenzene[14] *via* the sequence (*S*)-*N*-(2-nitro-5-bromophenyl)-α-alanine, (*S*)-3-methyl-6-bromo-3,4-dihydro-2(1*H*)-quinoxalinone, (*S*)-2-methyl-7-bromo-1,2,3,4-tetrahydroquinoxaline, and (*S*)-2-methyl-1,2,3,4-tetrahydroquinoxaline has been reported,[15] and was repeated using 2,5-dibromonitrobenzene[16] in place of 2,4-dibromonitrobenzene, *via* the parallel sequence, (*S*)-**8**, (*S*)-**9**, (*S*)-**10**, (*S*)-**1a**. Both sequences gave almost the same overall yields of (*S*)-**1a** of identical physical and optical properties, thus confirming the optical purity of the original unequivocally prepared (*S*)-**1a**.

Little difference was noted in the reactivities of the two series of bromo-substituted isomers. Curiously, (*S*)-3-methyl-6-bromo-3,4-dihydro-2(1*H*)-quinoxalinone was sta-

Table III
Chemical Shifts and Shift Differences of 2-Methyltetrahydroquinoxaline and Its Mono- and Diacyl Derivatives

Compd[a]	C-3 protons δ_{ax}[b]	$\Delta\delta$[c]	δ_{eq}	$\Delta\delta$	C-2 proton δ	$\Delta\delta$
4-Ac-2-Me-THQx	2.96	0.04	4.35	1.09	3.56	0.14
2-Me-THQx	2.92	−0.10	3.26	1.64	3.42	1.48
DiAc-2-Me-THQx	2.82		4.90		4.90	
4-Bz-2-Me-THQx[d]	3.25	0.33	4.15	0.89	3.55	0.13
2-Me-THQx	2.92	0.56	3.26	1.30	3.42	1.64
DiBz-2-Me-THQx	3.48		4.56		5.06	

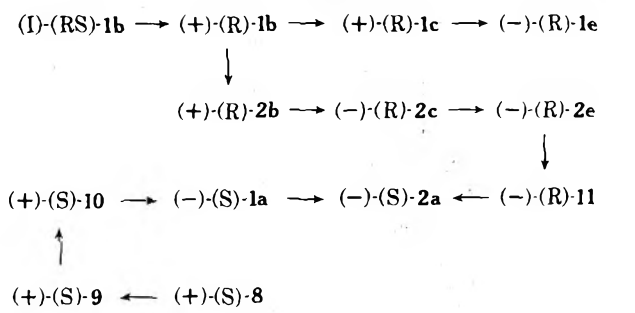
[a] THQx = tetrahydroquinoxaline, Ac = acetyl, Bz = benzoyl. [b] δ is in ppm from internal TMS for ~10% solutions in $CDCl_3$. [c] $-\Delta\delta$ represents an upfield shift. [d] Shift values are taken from ref 4.

ble in boiling water but dehydrogenated to 3-methyl-6-bromo-2(1*H*)-quinoxalinone[17] on heating or prolonged standing in organic solvents or on passage through an alumina column, whereas its isomer was stable in organic solvents but dehydrogenated to 3-methyl-7-bromo-2(1*H*)-quinoxalinone[17] in boiling water. The 4-acetyl-, 1,4-diacetyl-, and 1,4-dibenzoyl-(*S*)-2-methyl-1,2,3,4-tetrahydroquinoxalines have also been prepared.

It was desired to use this unequivocally prepared (S)-2-methyl-1,2,3,4-tetrahydroquinoxaline [(*S*)-**1a**] of known chirality about C-2 as a configurational standard to determine the chiralities of other 2-substituted 1,2,3,4-tetrahydroquinoxalines by means of a series of routine oxidation, reduction, and displacement reactions which would relate their absolute configurations to that of the standard, (*S*)-**1a**.

To this end, (*RS*)-1,2,3,4-tetrahydroquinoxaline-2-carboxamide[18] (**1b**) (from quinoxaline-2-carboxamide[19]) was resolved with dibenzoyl-*d*-tartaric acid,[20,21] thereby establishing the C-2 chiralities of amide **1b**, acid **1c**, and alcohol **1e** by relation to the configurational standard, (*S*)-2-methyl-1,2,3,4-tetrahydroquinoxaline [(S)-**1a**], as outlined in Scheme II.

Scheme II



Tosylation of the optically active amide (*R*)-**1b** with tosyl chloride in a buffered (pH 4) aqueous acetic acid–sodium acetate–tetrahydrofuran solution gave (+)-1-tosyl-1,2,3,4-tetrahydroquinoxaline-2-carboxamide [(*R*)-**2b**]. Hydrolysis of amide (*R*)-**2b** in aqueous sulfuric acid gave (−)-1-tosyl-1,2,3,4-tetrahydroquinoxaline-2-carboxylic acid [(*R*)-**2c**], and lithium aluminum hydride reduction of acid (*R*)-**2c** gave (−)-1-tosyl-2-hydroxymethyl-1,2,3,4-tetrahydroquinoxaline [(*R*)-**2e**]. In contrast to their untosylated parent analogs, the latter two compounds were stable crystalline solids. Treatment of alcohol (*R*)-**2e** with mesyl chloride in pyridine gave its (−)-*O*-mesylate derivative (*R*)-**11**, and sodium borohydride reduction of mesylate (*R*)-**11** gave (−)-(*S*)-1-tosyl-2-methyl-1,2,3,4-tetrahydroquinoxaline [(*S*)-**2a**], identical with that obtained by directly tosylating the configurational standard (*S*)-2-methyl-1,2,3,4-tetrahydroquinoxaline [(*S*)-**1a**].

Therefore, this sequence of reactions permitted assignment of the *R* chirality to the *O*-mesylate derivative **11** and the preceding 2-substituted 1,2,3,4-tetrahydroquinoxalines. It should be noted that the Cahn–Ingold–Prelog[22] designation of the chirality changes from *R* to *S* in going from the *O*-mesylate **11** to the methyl compound **2a**. The reason for this is that the priority of the groups changes in going from a hydroxymethyl mesyl group to a methyl group, although the arrangement of these groups about the chiral center remains the same.

Experimental Section[23]

1,2,3,4-Tetrahydroquinoxaline-2-carboxamide (1b). Catalytic reduction of quinoxaline-2-carboxamide[19] in EtOH over 10% Pd/C gave (*RS*)-**1b** (92%), recrystallized from $CHCl_3$–acetone (25 ml/g, 2:1) to constant mp 110–112° (lit.[18] mp 111°): nmr (DMSO-d_6) δ 3.22 (m, 2, NCH_2), 3.77 (m, 1, NCH), 5.28, 5.54 (br s, 2, NH's), 6.45 (s, 4, aromatic), 7.19 (br s, 2, $CONH_2$).

Resolution of (*RS*)-1b. To a hot (50°) solution of 26.6 g (0.15 mol) of amide (*RS*)-**1b** in 100 ml of Me_2CO was added a previously filtered, hot (50°) solution of 55.0 g (0.15 mol) of dibenzoyl-*d*-tartaric acid monohydrate in 500 ml of $CHCl_3$. After standing for 20 hr at room temperature, the solution was filtered to give 33.4 g of tan solid, mp 129–131°, $[\alpha]^{24}D$ −28.6° (*c* 1.0, EtOH). Four recrystallizations from hot Me_2CO (2 ml/g) diluted with $CHCl_3$ (6 ml/g) gave 20.3 g of light tan solid, mp 135–137°, $[\alpha]^{24}D$ −2.1° (*c* 1.0, EtOH), which analyzed for the 1.5 amide to 1.0 acid monohydrate complex.

Anal. Calcd for $(C_9H_{11}N_3O)_{1.5}\cdot C_{18}H_{14}O_8\cdot H_2O$: C, 58.89; H, 5.10; N, 9.86. Found: C, 58.87; H, 4.95; N, 9.75.

The diastereomeric salt (20.3 g) was dissolved in 50 ml of H_2O containing 10 g of $KHCO_3$. This aqueous solution was extracted for 12–18 hr with $CHCl_3$ in a continuous, heavier-than-water extractor. The extracts were dried ($MgSO_4$), concentrated to 20 ml, and cooled to give 7.43 g [55.8% of total (*R*)-**1b** enantiomer initially present] of light yellow solid, mp 122–124°, $[\alpha]^{24}D$ +162.0° (*c* 1.0, EtOH). Recrystallization from Me_2CO (3 ml/g) diluted with $CHCl_3$ (5 ml/g) gave light yellow (*R*)-**1b** of constant mp 123–124°: $[\alpha]^{24}D$ +162.8° (*c* 1.0, EtOH), +151.2° (c 1.0, THF), +174.8° (c 1.0, $CHCl_3$); ir (KBr) 3200, 3310, 3370, 3425 (NH), 1620 cm^{-1} (C=O); uv max 217 nm (ϵ 32,700), 249 (3890), 308 (3890); nmr, same as for the *RS* compound.

Anal. Calcd for $C_9H_{11}N_3O$: C, 61.00; H, 6.26; N, 23.71. Found: C, 60.90; H, 6.20; N, 23.63.

1,2,3,4-Tetrahydroquinoxaline-2-carboxylic Acid (1c). Hydrolysis of amide **1b** in refluxing 15% aq H_2SO_4 or 6 *N* HCl for 1 hr, followed by adjusting the pH to 4 with solid $KHCO_3$, gave acid **1c**.

(*RS*)-**1c.** A 92% yield was obtained: mp 165–167° (lit.[18] mp 166–168°); nmr (DMSO-d_6) δ 3.32 (d, J = 4.5 Hz, 2, NCH_2), 3.96 (t, J = 4.5 Hz, 1, NCH), 5.70 (m, COOH, NH's, and H_2O), 6.40 (m, 4, aromatic).

(*R*)-**1c.** A 62% yield was obtained: mp 185–186° (from H_2O, 20 ml/g); $[\alpha]^{24}D$ +36.1° (c 1.0, THF), +20.0° (c 1.0, EtOH), insoluble in $CHCl_3$; neut equiv, calcd 178.2, found 178.4; ir (KBr) 3370 (NH or OH), 3220 (OH or NH), 1690 cm^{-1} (C=O); nmr same as above.

Anal. Calcd for $C_9H_{10}N_2O_2$: C, 60.66; H, 5.66; N, 15.72. Found: C, 60.74; H, 5.45; N, 15.85.

2-Carboethoxy-1,2,3,4-tetrahydroquinoxaline (1d). Catalytic reduction of 2-carboethoxyquinoxaline[24] in EtOH over 10% Pd/C gave **1d** (90%), which was recrystallized from EtOH (6 ml/g) to constant mp 77–79° (lit.[18] mp 77°): nmr ($CDCl_3$) δ 1.22 (t, J = 7

Hz, 3, CH_3), 3.33 (2 d, J_{vic} = 6 Hz, J_{gem} = −11 Hz, 1, NCH_2 ax), 3.58 (2 d, J_{vic} = 4 Hz, J_{gem} = −11 Hz, 1, NCH_2 eq), 3.84 (s, 2, NH's), 4.01 (m, 1, NCH), 4.18 (q, J = 7 Hz, 2, OCH_2), 6.57 (m, 4, aromatic).

(*R*)-2-Hydroxymethyl-1,2,3,4-tetrahydroquinoxaline [(*R*)-1e]. Optically active (*R*)-**1e** was prepared in 99.3% yield by $LiAlH_4$ reduction of acid (*R*)-**1c** using the same procedure as reported[1a] for reduction of ester (*RS*)-**1d** to alcohol (*RS*)-**1e**: red oil; bp 230–260° (15 mm); $n^{25}D$ 1.6087; $[\alpha]^{24}D$ −24.2° (*c* 1.0, EtOH), −13.1° (*c* 1.0, THF), −25.8° (*c* 1.0, $CHCl_3$); ir, uv, and nmr same as for (*RS*)-**1e**.[1a]

1,2,3,4-Tetrahydroquinoline (4a). Catalytic reduction of redistilled quinoline in EtOH over 10% Pd/C gave **4a** in 66% yield: bp 142–144° (15 mm); $n^{21}D$ 1.5911 (lit.[25] bp 85–86° (2 mm), $n^{25}D$ 1.5910); nmr ($CDCl_3$) δ 1.88 (p, J = 6 Hz, 2, C-3 methylenes), 2.72 (t, J = 6 Hz, 2, C-4 methylenes), 3.23 (distorted t, J = 6 Hz, 2, C-2 methylenes), 3.55 (br s, 1, NH), 6.3–7.2 (m, 4, aromatic).

1,2,3,4-Tetrahydroquinaldine (4b). Catalytic reduction of redistilled quinaldine in EtOH over 10% Pd/C gave **4b** in 66% yield: bp 143–144° (20 mm); $n^{21}D$ 1.5687 (lit.[26] bp 76–78.5° (0.75 mm), $n^{20}D$ 1.5692); nmr ($CDCl_3$) δ 1.15 (d, J = 6.5 Hz, 3, CH_3), 1.72 (m, 2, C-3 methylenes), 2.68 (m, 2, C-4 methylenes), 3.32 (m, 1, C-2 methine), 3.47 (br s, 1, NH), 6.3–7.2 (m, 4, aromatic).

General Procedure for N-Tosylation in Acidic Medium. Ten millimoles of the compound to be tosylated and 1.5 g (11.0 mmol) of $NaOAc \cdot 3H_2O$ were dissolved in 15 ml of H_2O, 4 ml of THF, and 2 ml of gl HOAc (solution pH ~4) and cooled to 5° in an ice bath. TsCl (2.1 g, 11.0 mmol) was added, and the mixture was stirred overnight (~18 hr) while warming up to room temperature. The precipitated product was filtered and dried. If the product did not precipitate directly from the solution, excess H_2O was added, and the solution was extracted with $CHCl_3$, from which the product was isolated by evaporation of the $CHCl_3$ and crystallization of the residue.

1-*p*-Toluenesulfonyl-1,2,3,4-tetrahydroquinoxaline-2-carboxamide (2b). (*RS*)-2b. An 85% yield was obtained by tosylating (*RS*)-**1b**: white solid; mp 182–183°, recrystallized from EtOH (3 ml/g); ir (KBr) 3470, 3360, 3310 (NH), 1665 (C=O), 1345, 1165 cm^{-1} (CSO_2); uv max 213 nm (ε 39,400), 237 sh (19,400), 303 (4130); nmr (DMSO-d_6) δ 2.31 (s, 3, $TsCH_3$), 3.32 (m, 2, NCH_2), 4.26 (m, 1, NCH), 6.05 (br s, 1, NH), 6.40–7.70 (m, 10, aromatic and $CONH_2$); nmr (acetone-d_6) δ 2.31 (s, 3, $TsCH_3$), 3.41 (m, 2, NCH_2), 4.24 (t, J = 10 Hz, 1, NCH), 5.42 (br s, 1, NH), 6.45–7.65 (m, 10, aromatic and $CONH_2$).

Anal. Calcd for $C_{16}H_{17}N_3O_3S$: C, 57.99; H, 5.17; N, 12.68. Found: C, 57.99; H, 5.06; N, 12.86.

(*R*)-2b. An 80.5% yield was obtained by tosylating (*R*)-**1b**: mp 155–156°; $[\alpha]^{24}D$ +44.4° (*c* 1.0, $CHCl_3$), +10.0° (*c* 1.0, THF), +19.8° (*c* 1.0, EtOH); ir (KBr) 3450, 3390, 3125 (NH), 1670 (C=O), 1335, 1160 cm^{-1} (CSO_2); uv max 214 nm (ε 26,000), 238 sh (13,000), 305 (2890); nmr same as for (*RS*)-**2b**.

Anal. Found: C, 58.06; H, 5.12; N, 12.41.

1-*p*-Toluenesulfonyl-1,2,3,4-tetrahydroquinoxaline-2-carboxylic Acid (2c). (*RS*)-2c. A 67% yield was obtained by tosylating (*RS*)-**1c**: white solid; mp 189–190°, recrystallized from MeOH-H_2O (6 ml/g, 2:1); ir (KBr) 3380 (NH), 3290 (OH), 1750 (C=O), 1330, 1140 cm^{-1} (CSO_2); uv max 213 nm (ε 20,800), 238 (12,500), 304 (2330); nmr (DMSO-d_6) δ 2.32 (s, 3, $TsCH_3$), 3.44 (m, 2, NCH_2), 4.18 (m, 1, NCH), 5.9–7.2 (m, 10, aromatic, NH, and COOH); neut equiv calcd 332.4, found 332.7.

Anal. Calcd for $C_{16}H_{16}N_2O_4S$: C, 57.82; H, 4.85; N, 8.43. Found: C, 57.71; H, 4.89; N, 8.56.

(*R*)-2c. Amide (*R*)-**2b** was hydrolyzed in refluxing 15% H_2SO_4 for 2.5 hr to give acid (*R*)-**2c** in 94.7% yield: mp 123–125°; $[\alpha]^{24}D$ −21.3° (*c* 1.0, THF), −34.4° (*c* 1.0, EtOH), unstable in $CHCl_3$ solution; neut equiv, calcd 332.4, found 332.7; ir (KBr) 3370 (NH), 3650–2800 (OH), 1710, 1738 (d, C=O), 1340, 1160 cm^{-1} (CSO_2); uv and nmr same as for (*RS*)-**2c**.

Anal. Found: C, 57.65; H, 4.97; N, 8.33.

1-*p*-Toluenesulfonyl-2-carboethoxy-1,2,3,4-tetrahydroquinoxaline (2d). An 84% yield was obtained by tosylating **1d**: white solid; mp 139–140°, recrystallized from EtOH (10 ml/g); ir (KBr) 3370 (NH), 1740 (C=O), 1350, 1160 cm^{-1} (CSO_2); uv max 200 nm (end absorption), 215 (ε 23,700), 240 (12,300), 307 (3150); nmr ($CDCl_3$) δ 1.27 (t, J = 7 Hz, 3, CH_3), 2.36 (s, 3, $TsCH_3$), 3.04 (2 d, J_{vic} = 10 Hz, J_{gem} = −13 Hz, 1, NCH_2 ax), 3.44 (m, 1, NCH eq), 4.21 (q, J = 7 Hz, 2, OCH_2), 4.38 (s, 1, NH), 4.58 (2 d, J = 3 and 13 Hz, 1, NCH), 6.4–7.8 (m, 8, aromatic).

Anal. Calcd for $C_{18}H_{20}N_2O_4S$: C, 59.98; H, 5.59; N, 7.77. Found: C, 60.06; H, 5.59; N, 7.79.

1-*p*-Toluenesulfonyl-2-hydroxymethyl-1,2,3,4-tetrahydroquinoxaline (2e). (*RS*)-2e. A 91% yield was obtained by tosylating (*RS*)-**1e**: white solid; mp 147.5–148.5°, recrystallized from EtOH (5 ml/g); nmr ($CDCl_3$) δ 2.35 (s, 3, $TsCH_3$), 3.26 (m, 2, NCH_2), 3.47 (m, 2, CH_2O), 4.11 (m, 1, NCH), 2.9–3.6 (m, 2, OH and NH), 6.4–7.7 (m, 8, aromatic); ir and uv reported previously.[1a]

(*R*)-2e. To a stirred suspension of 0.76 g (20.0 mmol) of $LiAlH_4$ in 25 ml of dry Et_2O was added dropwise over 0.25 hr a solution of 0.90 g (2.7 mmol) of tosyl acid (*R*)-**2c** in 6 ml of dry THF. The solution was refluxed for 1.5 hr and cooled in an ice bath. Excess $LiAlH_4$ was destroyed by successive, dropwise addition of 0.76 ml of H_2O, 0.57 ml of 20% NaOH, and 2.7 ml of H_2O, followed by 25 ml of $CHCl_3$ to extract the organic product. After refluxing for 1.5 hr, the solution was filtered. The filtrate was dried ($MgSO_4$), treated with Norit and Celite, and evaporated under vacuum (30°) to give 0.80 g (93.3%) of yellow oil, which upon recrystallization from C_6H_6 (5 ml/g) gave a white solid, mp 113–115° with a phase change at 76–78° (probably due to a benzene solvate). Thorough drying of the solid under vacuum at 60° gave a sharp melting point of 114–115°; $[\alpha]^{24}D$ −22.4° (*c* 1.0, $CHCl_3$), −43.0° (*c* 1.0, THF), −64.0° (*c* 1.0, EtOH); ir (KBr) 3392 (NH), 3500–3100 (br, OH), 1330, 1155 cm^{-1} (CSO_2); uv and nmr same as above.

Anal. Calcd for $C_{16}H_{18}N_2O_3S$: C, 60.36; H, 5.70; N, 8.80. Found, C, 60.42; H, 5.48; N, 8.75.

1-*p*-Toluenesulfonyl-1,2,3,4-tetrahydroquinoline (5a). An 85% yield was obtained by tosylating **4a**: white solid; mp 95–96° (lit.[6] mp 93–94°) recrystallized from EtOH (2 ml/g); ir (KBr) 1345, 1155 cm^{-1} (CSO_2); uv max 200 nm (end absorption), 208 (ε 11,200), 219 sh (4600), 253 (5830); nmr ($CDCl_3$) δ 1.62 (p, J = 6 Hz, 2, C-3 methylenes), 2.34 (s, 3, $TsCH_3$), 2.43 (t, J = 6 Hz, 2, C-4 methylenes), 3.78 (distorted t, J = 6 Hz, 2, C-2 methylenes), 6.9–7.9 (m, 8, aromatic).

1-*p*-Toluenesulfonyl-1,2,3,4-tetrahydroquinaldine (5b). A 72% yield was obtained by tosylating **4b**: white solid; mp 84–85° recrystallized from EtOH (2 ml/g); ir (KBr) 1337, 1155 cm^{-1} (CSO_2); uv max 200 nm (end absorption), 250 (ε 9320); nmr ($CDCl_3$) δ 1.26 (d, J = 6.5 Hz, 3, CH_3), 1.1–2.6 (m, 4, C-3, C-4 methylenes), 2.35 (s, 3, $TsCH_3$), 4.38 (sextet, J = 6.5 Hz, 1, C-2 methine), 6.9–7.9 (m, 8, aromatic).

Anal. Calcd for $C_{17}H_{19}NO_2S$: C, 67.75; H, 6.35; N, 4.65. Found: C, 67.67; H, 6.35; N, 4.50.

Benzo[*b*]-4-*p*-toluenesulfonyl-1,4-diazabicyclo[3.1.1]hept-6-one (Lactam 3). To 0.89 g (50.0 mmol) of acid **1c** in 3 ml of dry C_5H_5N cooled to 5° was added 2.10 g (11.0 mmol) of TsCl. After being stirred for 15 min, the solution was poured over 10 ml of ice and H_2O and filtered to give 1.27 g (80.9%) of yellow solid, mp 110–130° (lactam **3**). Acidification of the filtrate to pH 2 with 10% H_2SO_4 gave 0.35 g (21.1%) of pink solid, mp 100–130° (tosyl acid **2c**). The lactam **3** product was triturated with 10 ml of 1 *N* NaOH and filtered to give 1.13 g (72.0%) of yellow solid, mp 180–200°. Recrystallization from EtOH-$CHCl_3$ (50 ml/g, 2:1) gave white crystals of constant mp 213–214°: ir (KBr) 1690 (C=O), 1345, 1165 cm^{-1} (CSO_2), neither OH nor NH; uv max 200 nm (end absorption), 223 (ε 24,300); nmr ($CDCl_3$) δ 2.42 (s, 3, $TsCH_3$), 3.35–4.65 (m, 3, NCH_2 and NCH), 7.1–8.3 (m, 8, aromatic).

Anal. Calcd for $C_{16}H_{14}N_2O_3S$: C, 61.13; H, 4.49; N, 8.91. Found: C, 61.21; H, 4.53; N, 8.80.

Hydrolysis of Lactam 3. Lactam **3** (0.16 g, 0.51 mmol) was refluxed for 5 hr in 10 ml of 1 *N* NaOH. After clarification with Norit and Celite, the solution was acidified with 6 *N* HCl and filtered to give 0.08 g (47.3%) of tan solid, mp 168–172°. This was recrystallized from MeOH-H_2O (6 ml/g, 2:1) to constant mp 188–190°, identical with acid **2c** by ir and mixture melting point.

***N*-(2-Nitro-4-bromophenyl)-α-alanine (8).** This was prepared in 35% yield from α-alanine and 2,5-dibromonitrobenzene by the procedure reported previously[15] for its isomer, and was recrystallized from C_6H_6 (40 ml/g).

(*S*)-8: mp 165–167°; ir (KBr) 3380 (NH), 1717 (C=O), 508 cm^{-1} (CBr); uv max 204 nm (ε 13,300), 239 (37,500), 274 sh (9100), 432 (8380); $[\alpha]^{24}D$ +16.3° (*c* 1.0, THF).

Anal. Calcd for $C_9H_9N_2O_4Br$: C, 37.39; H, 3.14; N, 9.69. Found: C, 37.75; H, 3.16; N, 9.60.

(*RS*)-8: mp 165–167° (lit.[17] mp 162–164°); ir, uv, and nmr same as above.

3-Methyl-7-bromo-3,4-dihydro-2(1*H*)-quinoxalinone (9). This was prepared from **8** in 73% yield by $SnCl_2$ reduction and in 86% yield by Raney nickel catalytic reduction as reported previously[15] for its isomer and was recrystallized from $CHCl_3$-ligroin (20 ml/g, 1:1).

(*S*)-9: mp 169–171°; ir (KBr) 3350 (NH), 1670 (C=O), 560 cm^{-1} (CBr); uv max 225 nm (ε 43,700), 274 (3570), 316 (4484); nmr

($CDCl_3$–DMSO-d_6, 1:1) δ 1.34 (d, J = 7 Hz, 3, CH_3), 3.30 (br s, 1, NH), 3.86 (q, J = 7 Hz, 1, NCH), 5.64 (br s, 1, COHN), 6.5–7.0 (m, 3, aromatic); $[\alpha]^{24}D$ +52.9° (*c* 1.0, THF).

Anal. Calcd for $C_9H_9N_2OBr$: C, 44.84; H, 3.76; N, 11.62. Found: C, 44.77; H, 3.60; N, 11.70.

(*RS*)-**9**: mp 163–164°; ir, uv, and nmr same as above.

Anal. Found: C, 44.88; H, 3.75; N, 11.73.

2-Methyl-6-bromo-1,2,3,4-tetrahydroquinoxaline (10). This was prepared in 56% yield by $LiAlH_4$ reduction of **9** by the procedure reported previously[15] for its isomer and was recrystallized from ligroin (50 ml/g).

(*S*)-**10**: mp 124–125.5°; ir (KBr) 3330, 3380 (NH), 566 cm^{-1} (CBr); uv max 222 nm (ϵ 39,700), 265 (6140), 322 (3860); nmr ($CDCl_3$–DMSO-d_6, 1:1) δ 1.16 (d, J = 6 Hz, 3, CH_3), 2.60–3.50 (m, 3, NCH and NCH_2), 5.06, 5.30 (2 br s, 2, NH's), 6.25–6.57 (m, 3, aromatic); $[\alpha]^{24}D$ + 14.3° (*c* 1.0, THF).

Anal. Calcd for $C_9H_{11}N_2Br$: C, 47.60; H, 4.88; N, 12.33. Found: C, 47.63; H, 4.77; N, 12.03.

(*RS*)-**10**: mp 154–155°; ir, uv, and nmr same as above.

Anal. Found: C, 47.47; H, 4.82; N, 12.43.

1,4-Diacetyl-2-methyl-6-bromo-1,2,3,4-tetrahydroquinoxaline. This was prepared in 90% yield from **10** by the procedure reported previously[15] and was recrystallized from ligroin (40 ml/g).

(*S*): mp 143–144°; ir (KBr) 1650 (C=O), 595 cm^{-1} (CBr); uv max 232 nm (ϵ 21,000), 258 (11,300); nmr ($CDCl_3$) δ 1.17 (d, J = 6.5 Hz, 3, CH_3), 2.17, 2.24 (2 s, 6, $COCH_3$), 2.98 (2 d, J_{vic} = 6 Hz, J_{gem} = −12 Hz, 1, NCH_2 ax), 4.4–5.3 (m, 2, NCH, NCH_2 eq), 7.1–7.8 (m, 4, aromatic); $[\alpha]^{24}D$ +95.9° (*c* 1.0, THF).

Anal. Calcd for $C_{13}H_{15}N_2O_2Br$: C, 50.18; H, 4.86; N, 9.00. Found: C, 49.90; H, 4.85; N, 9.03.

(*RS*): mp 157–159°; ir, uv, and nmr same as above.

Anal. Found: C, 50.39; H, 4.53; N, 8.96.

2-Methyl-1,2,3,4-tetrahydroquinoxaline (1a). Catalytic reduction of 2-methylquinoxaline[27] in 95% EtOH over 10% Pd/C catalyst gave (*RS*)-**1a** (82%), which was recrystallized from ligroin (20 ml/g) to constant mp 70–71° (lit.[15,28] mp 70–71°; lit.[29] mp 71°; lit.[30] mp 72°); nmr ($CDCl_3$) δ 1.12 (d, J = 6 Hz, 3, CH_3), 2.92 (2 d, J_{vic} = 8 Hz, J_{gem} = −11 Hz, 1, NCH_2 ax), 3.26 (2 d, J_{vic} = 3 Hz, J_{gem} = −11 Hz, 1, NCH_2 eq), 3.42 (m, 1, NCH), 3.47 (s, 2, NH's), 6.52 (m, 4, aromatic).

(*S*)-**1a.** This was prepared in 68.6% yield by catalytic hydrogenolysis of the bromo group of 2-methyl-6-bromo-1,2,3,4-tetrahydroquinoxaline (**10**) by the procedure reported previously:[15] mp 90–90.5°; $[\alpha]^{24}D$ +60.0° (*c* 1.0, THF), −6.1° (*c* 1.0, $CHCl_3$), −35.8° (*c* 1.0, EtOH); ir, uv, nmr, and analyses have been reported previously.[15]

4-Acetyl-2-methyl-1,2,3,4-tetrahydroquinoxaline (6a). Ac_2O (1 ml, 10 mmol) was added dropwise with shaking to 0.26 g (1.76 mmol) of **1a**. The solid dissolved with evolution of heat and then reprecipitated, giving **6a** (93% yield), which was recrystallized from $CHCl_3$–ligroin (45 ml/g, 1:2) to constant melting point.

(*RS*)-**6a**: white solid; mp 175–177°; ir (KBr) 3310 (NH), 1620 cm^{-1} (C=O); uv max 224 nm (ϵ 25,400), 246 sh (15,200); nmr ($CDCl_3$, 100 MHz) δ 1.18 (d, J = 6 Hz, 3, CH_3), 2.25 (s, 3, $COCH_3$), 2.96 (2 d, J_{vic} = 8 Hz, J_{gem} = −12 Hz, 1, NCH_2 ax), 3.56 (m, 1, NCH), 4.10 (br s, 1, NH), 4.35 (2 d, J = 4 Hz, J_{gem} = −12 Hz, 1, NCH_2 eq), 6.4–7.2 (m, 4, aromatic); decoupling of the multiplet at δ 3.56 collapsed the methyl doublet at δ 1.18 into a singlet.

Anal. Calcd for $C_{11}H_{14}N_2O$: C, 69.45; H, 7.42; N, 14.72. Found: C, 69.68; H, 7.52; N, 14.89.

(*S*)-**6a**: mp 202.5–204.5°; $[\alpha]^{24}D$ −177° (*c* 1.0, $CHCl_3$), −141° (*c* 1.0, THF), −122° (*c* 1.0, EtOH); ir, uv, and nmr same as above.

Anal. Found: C, 69.34; H, 7.39; N, 14.67.

1,4-Diacetyl-2-methyl-1,2,3,4-tetrahydroquinoxaline (7a). A solution of 0.11 g (0.74 mmol) of **1a** in 1.0 ml (10 mmol) of Ac_2O was allowed to stand at room temperature for 24 hr. Excess Ac_2O was destroyed by addition of 1.5 ml of H_2O, and evaporation of the solvents under vacuum (40°) gave a 93% yield of the product which was recrystallized from ligroin (75 ml/g).

(*RS*)-**7a**: mp 141–143° (lit.[24] mp 138–139°); ir (KBr) 1650 cm^{-1} (C=O); uv max 226 nm (ϵ 23,200), 251 (12,300); nmr ($CDCl_3$, 100 MHz) δ 1.13 (d, J = 6 Hz, 3, CH_3), 2.16, 2.20 (2 s, 6, $COCH_3$), 2.82 (m, 1, NCH_2 ax), 4.90 (m, 2, NCH and NCH_2 eq), 7.25 (m, 4, aromatic); decoupling of the multiplet at δ 4.90 collapsed the methyl doublet at δ 1.13 into a singlet.

(*S*)-**7a**: mp 143–144°; $[\alpha]^{24}D$ +127° (*c* 1.0, $CHCl_3$), +133° (*c* 1.0, THF), +138° (*c* 1.0, EtOH); ir, uv, and nmr same as above.

Anal. Calcd for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.94; N, 12.06. Found: C, 67.23; H, 6.90; N, 12.13.

1,4-Dibenzoyl-2-methyl-1,2,3,4-tetrahydroquinoxaline (7b). To 0.13 g (0.88 mmol) of **1a** suspended in 5 ml of 10% NaOH was added dropwise with shaking 0.5 ml (0.61 g, 4.2 mmol) of PhCOCl. The solution was diluted with 5 ml of H_2O, cooled, and filtered to give 0.30 g (95.8%) of white solid, which was recrystallized from EtOH (15 ml/g).

(*RS*)-**7b**: mp 186–187° (lit.[4] mp 187°); ir (KBr) 1640 cm^{-1} (C=O); uv max 200 nm (end absorption), 219 sh (ϵ 19,800), 270 (10,400); nmr ($CDCl_3$) δ 1.29 (d, J = 6 Hz, 3, CH_3), 3.48 (2 d, J_{vic} = 6 Hz, J_{gem} = −13 Hz, 1, NCH_2 ax), 4.56 (d, J_{vic} = 6 Hz, J_{gem} = −13 Hz, 1, NCH_2 eq), 5.06 (p, 1, NCH), 6.83 (m, 4, Qx aromatic), 7.45 (m, 10, Ph aromatic).

Anal. Calcd for $C_{23}H_{20}N_2O_2$: C, 77.51; H, 5.66; N, 7.86. Found: C, 77.53; H, 5.63; N, 7.84.

(*S*)-**7b**: mp 186–187°; $[\alpha]^{24}D$ +144° (*c* 1.0, $CHCl_3$), +123° (*c* 1.0, THF), +123° (*c* 1.0, EtOH); ir, uv, and nmr same as above.

Anal. Found: C, 77.17; H, 5.61; N, 7.67.

(*R*)-1-*p*-Toluenesulfonyl-2-hydroxymethyl-1,2,3,4-tetrahydroquinoxaline Methanesulfonate [(*R*)-11]. To a stirred, cold (−5°) solution of 0.5 ml (0.75 g, 6.5 mmol) of MsCl in 2 ml of dry C_5H_5N was added dropwise over 0.2 hr a solution of 0.68 g (2.14 mmol) of alcohol (*R*)-**1e** in 3 ml of dry C_5H_5N. After being stirred for 3 hr while cold, the solution was diluted with 30 ml of ice-water and cooled, causing a red oil to separate out. The solution was acidified with HCl and extracted with $CHCl_3$. The $CHCl_3$ extracts were dried ($MgSO_4$), treated with Norit and Celite, concentrated to 4 ml, and diluted with 2 ml of ligroin to give 0.17 g (20.1%) of white solid, mp 129–131°, $[\alpha]^{24}n$ −30.4° (*c* 1.0, $CHCl_3$). Recrystallization from $CHCl_3$–ligroin (20 ml/g, 2:1) gave white solid of constant mp 136–137°; $[\alpha]^{24}D$ −34.3° (*c* 1.0, $CHCl_3$), −40.7° (*c* 1.0, THF), −60.7° (*c* 1.0, EtOH); uv max 200 nm (end absorption), 215 (ϵ 30,900), 239 (16,200), 310 (1880); ir and nmr same as (*RS*)-**11** reported previously.[1a]

Anal. Calcd for $C_{17}H_{20}N_2O_5S_2$: C, 51.50; H, 5.08; N, 7.07. Found: C, 51.42; H, 4.94; N, 7.16.

1-*p*-Toluenesulfonyl-2-methyl-1,2,3,4-tetrahydroquinoxaline (2a). (*RS*)-**2a.** A 60% yield was obtained by tosylating **1a**: white solid; mp 146–147°, recrystallized from EtOH (15 ml/g); ir (KBr) 3390 (NH), 1330, 1160 cm^{-1} (CSO_2); uv max 215 nm (ϵ 25,000), 244 (13,000), 311 (3260); nmr ($CDCl_3$) δ 1.00 (d, J = 6 Hz, 3, CH_3), 2.34 (s, 3, $TsCH_3$), 2.78 (t, J = 2.5 Hz, 1, NCH_2 ax), 2.91 (t, J = 2.5 Hz, 1, NCH_2 eq), 3.65 (m, 1, NH), 4.15 (m, 1, NCH), 6.36–7.77 (m, 8, aromatic).

Anal. Calcd for $C_{16}H_{18}N_2O_2S$: C, 63.55; H, 6.00; N, 9.26. Found: C, 63.58, H, 5.93; N, 9.04.

(*S*)-2a. A. By Reduction of the Mesylate (*R*)-11. A solution of 0.09 g (0.227 mmol) of mesylate (*R*)-11 and 0.04 g (1.0 mmol) of $NaBH_4$ in 2.5 ml of THF was refluxed for 4 hr. After cooling, the solution was diluted with 0.25 ml of H_2O and 1 drop of 6 *N* NaOH. The layers were separated; the organic layer was dried ($MgSO_4$) and evaporated under vacuum (30°) to give 0.08 g of clear oil. Crystallization of the oil from 0.25 ml of EtOH gave 0.04 g (58.4%) of white solid, mp 112–114°. Recrystallization from EtOH (15 ml/g) gave white solid of mp 115–117°; $[\alpha]^{24}D$ −38.0° (*c* 1.0, THF), −62.2° (*c* 1.0, EtOH); identical by ir and mixture melting point with (*S*)-2a obtained by directly tosylating (*S*)-2-methyl-1,2,3,4-tetrahydroquinoxaline [(*S*)-**1a**] by method B below.

(*S*)-2a. B. By Tosylation of (*S*)-2-Methyl-1,2,3,4-tetrahydroquinoxaline. Tosylation of (*S*)-**1a** gave (*S*)-**2a** in 59.5% yield as a white solid which was recrystallized from EtOH (15 ml/g) to constant mp 116.5–117°; $[\alpha]^{24}D$ −37.4° (*c* 1.0, THF), −60.6° (*c* 1.0, EtOH), −32.7° (*c* 1.0, $CHCl_3$); uv max 215 nm (ϵ 18,000), 243 (9390), 312 (1970); ir and nmr same as for (*RS*)-**2a**.

Anal. Found: C, 63.73; H, 6.05; N, 9.25.

Acknowledgment. We thank Dr. Ronald Block of the Papanicoloau Cancer Research Institute, Miami, Florida, for the 100-MHz nmr decoupling experiments and for enlightening discussions of same.

Registry No. (*RS*)-**1a**, 49849-47-0; (*S*)-**1a**, 24463-31-8; (*R*)-**1b**, 49849-48-1; (*RS*)-**1b**, 49849-49-2; (*RS*)-**1b** dibenzoyl-*d*-tartrate, 49776-49-0; (*R*)-**1c**, 49849-50-5; (*RS*)-**1c**, 49849-51-6; (*RS*)-**1d**, 49849-52-7; (*R*)-**1e**, 49849-53-8; (*RS*)-**2a**, 49849-54-9; (*S*)-**2a**, 49849-55-0; (*R*)-**2b**, 49849-56-1; (*RS*)-**2b**, 49849-57-2; (*R*)-**2c**, 49849-58-3; (*RS*)-**2c**, 49849-59-4; (*RS*)-**2d**, 49849-60-7; (*R*)-**2e**, 49849-61-8; (*RS*)-**2e**, 49849-62-9; **3**, 49849-63-0; **4a**, 635-46-1; **4b**, 1780-19-4; **5a**, 24310-24-5; **5b**, 49849-64-1; (*RS*)-**6a**, 49849-65-2; (*S*)-**6a**, 49849-66-3; (*RS*)-**7a**, 49849-67-4; (*S*)-**7a**, 24463-32-9; (*RS*)-**7b**, 49849-68-5; (*S*)-**7b**, 49849-69-6; (*S*)-**8**, 49849-70-9; (*RS*)-**9**, 49849-71-0; (*S*)-**9**, 49849-72-1; (*RS*)-**10**, 49849-73-2; (*S*)-**10**, 49849-

74-3; (*R*)-11, 49776-50-3; quinoxaline-2-carboxamide, 5182-90-1; 2-carboethoxyquinoxaline, 7065-23-8; quinoline, 91-22-5; quinaldine 91-63-4; (*RS*)-1,4-diacetyl-2-methyl-6-bromo-1,2,3,4-tetrahydroquinoxaline, 49849-75-4; (*S*)-1,4-diacetyl-2-methyl-6-bromo-1,2,3,4-tetrahydroquinoxaline, 49849-76-5.

References and Notes

(1) (a) Part XXI of this series: G. H. Fisher and H. P. Schultz, *J. Org. Chem.*, **39**, 631 (1974); (b) NSF Trainee 1969–1972; abstracted from the Ph.D. dissertation of G. H. F.
(2) S. J. Benkovic, P. A. Benkovic, and D. R. Comfort, *J. Amer. Chem. Soc.*, **91**, 5270 (1969); S. J. Benkovic, P. A. Benkovic, and R. Chrzanowski, *ibid.*, **92**, 523 (1970); S. J. Benkovic, W. P. Bullard, and P. A. Benkovic, *ibid.*, **94**, 7542 (1972).
(3) M. P. Mertes and A. J. Lin, *J. Med. Chem.*, **13**, 77 (1970).
(4) R. Aguilera, J.-C. Duplan, and C. Nofre, *Bull. Soc. Chim. Fr.*, 4491 (1968).
(5) E. Campaigne, N. F. Chamberlain, and B. E. Edwards, *J. Org. Chem.*, **27**, 135 (1962).
(6) V. A. Zagorevskii and N. V. Dudykina, *Zh. Obshch. Khim.*, **34**, 2282 (1964); *Chem. Abstr.*, **61**, 11960*f* (1964).
(7) K. Nagarajan, M. D. Nair, and P. M. Pillai, *Tetrahedron*, **23**, 1683 (1967).
(8) H. Booth, *J. Chem. Soc.*, 1841 (1964).
(9) J. S. Morley, *J. Chem. Soc.*, 4002 (1952).
(10) J. C. Cavagnol and F. Y. Wiselogle, *J. Amer. Chem. Soc.*, **69**, 795 (1947).
(11) D. P. N. Satchell, *Quart. Rev. (London)*, **17**, 160 (1963).
(12) R. A. Archer and H. S. Mosher, *J. Org. Chem.* **32**, 1378 (1967).
(13) D. G. Lister and J. K. Tyler, *Chem. Commun.*, 152 (1966).
(14) A. F. Holleman, *Recl. Trav. Chim.*, **25**, 183 (1906).
(15) G. H. Fisher, P. J. Whitman, and H. P. Schultz, *J. Org. Chem.*, **35**, 2240 (1970).
(16) G. S. Hammond and F. J. Modic, *J. Amer. Chem. Soc.*, **75**, 1385 (1953).
(17) R. Van Dusen and H. P. Schultz, *J. Org. Chem.*, **21**, 1326 (1956).
(18) G. F. Bettinetti, *Ann. Chim. (Rome)*, **51**, 920 (1961); *Chem. Abstr.*, **57**, 5914c (1962).
(19) F. Minisci, G. P. Gardini, R. Galli, and F. Bertini, *Tetrahedron Lett.*, 15 (1970).
(20) C. L. Butler and L. H. Cretcher, *J. Amer. Chem. Soc.*, **55**, 2605 (1933).
(21) M. Semonsky, A. Cerny, and V. Zikan, *Chem. Listy*, **50**, 116 (1956); *Collect. Czech. Chem. Commun.*, **21**, 382 (1956); *Chem. Abstr.*, **50**, 13059a (1956).
(22) R. S. Cahn, C. K. Ingold, and V. Prelog, *Experientia*, **12**, 81 (1956).
(23) Melting points, uncorrected, were determined on a Thomas-Hoover apparatus. Spectra were recorded as follows: uv, Jasco ORD/UV-5 in 95% ethanol in 1-cm quartz cells; H nmr, Hitachi Perkin-Elmer R-20, 60 MHz, 34°, or Varian Associates HA-100D-15, 100 MHz, 26°, δ in ppm from internal TMS; ir, Beckman IR-10. All optical activities were recorded on a Rudolph Model 63 polarimeter. Elemental analyses were performed by PCR, Inc., Gainesville, Fla. Ligroin was medium boiling, bp 66–75°, and EtOH was 95%. Tosyl chloride was recrystallized from THF. Pyridine was redistilled from CaH_2 and stored over NaOH pellets. Anhydrous ether was dried over $LiAlH_4$.
(24) A. S. Elina and O. Yu. Magidson, *J. Gen. Chem. USSR*, **25**, 145 (1955); *Chem. Abstr.*, **50**, 1839*g* (1956).
(25) H. Adkins and H. R. Billica, *J. Amer. Chem. Soc.*, **70**, 695 (1948).
(26) W. L. Graef, J. C. Cannon, and J. P. Buckley, *J. Med. Chem.*, **8**, 260 (1965).
(27) K. Böttcher, *Ber.*, **46**, 3084 (1913).
(28) M. Munk and H. P. Schultz, *J. Amer. Chem. Soc.*, **74**, 3433 (1952).
(29) S. Maffei and S. Pietra, *Gazz. Chim. Ital.*, **88**, 556 (1958); *Chem. Abstr.*, **53**, 20060*d* (1959).
(30) C. Ris, *Ber.*, **21**, 383 (1888).

Sigmatropic Rearrangement of Unsaturated Acetals. A Mechanistic Study of the Thermal Isomerization of 5-Alkylidene-1,3-dioxanes

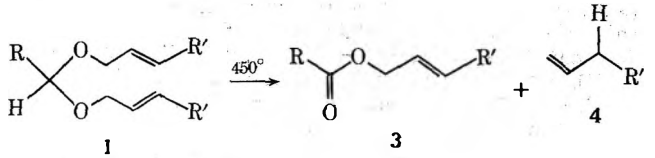
F. Mutterer and J. P. Fleury*

Laboratoire de Chimie Organique Générale,[1] Ecole Supérieure de Chimie, 68093 Mulhouse Cedex, France

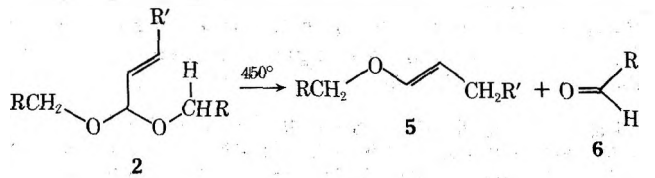
Received July 27, 1973

The preparation and pyrolysis of 2-*tert*-butyl-5-ethylidene-1,3-dioxane-2-*d* are described. A negative isotope crossover experiment and a deuterium kinetic isotopic effect are in favor of an intramolecular isomerization involving a concerted 1,5-hydrogen shift. Some conclusions on the transition state are discussed.

We have shown that unsaturated acetals undergo two types of thermal cleavage depending on the location of the double bond.[2] The acetals of type 1 derived from allylic alcohols cleave thermally to give allylic esters 3 and olefins 4. On the other hand, those acetals 2 derived from α,β-unsaturated aldehydes fragment to vinyl ethers 5 and saturated aldehydes 6.

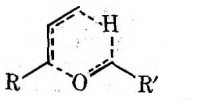


1 3 4



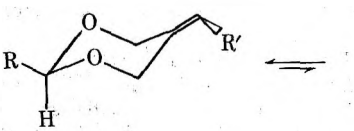
2 5 6

Both cleavages can be described as retro-ene reactions[3a] or retrograde $_\pi2_a2_s + {}_\pi2_s$ cycloadditions in which a heteroatom is involved. For acyclic acetals, the results of kinetic studies in the gas-phase pyrolysis[3b] (first-order kinetics with a negative activation entropy) unambiguously support a concerted [1,5] sigmatropic hydrogen migration. The structures of cleavage products are in agreement with such a mechanism. The experimental data available to date suggest that a six-membered transition state (such as **7a** or **7b**) is involved in the thermolysis.

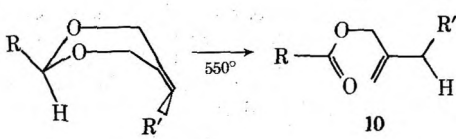


7a, R = O-alkyl; R′ = H, alkyl
b, R = H; R′ = O-alkyl

Insofar as acyclic acetals are concerned, there is no steric restriction to such a transition state. In cyclic acetals, such as 5-alkylidene-1,3-dioxanes 8, the concerted [1,5] sigmatropy, as proposed above, imposes considerable strain on the less favored[4] boat conformer 9. Dreiding



8



9 10

Table I
The Kinetic Isotopic Effect in the Pyrolysis of 18

Conditions of pyrolysis[a]	Deuterium content, %: Starting dioxane 18, D_s	Recovered dioxane 18, D_r	Ester 20	k_H/k_D[b] at 510°
510, 45 sec, 50%	36.4	49.4	28.5	2.3
510, 45 sec, 45%	20.6	30.9	12.4	3.9

[a] Temperature (°C), contact time in seconds, total conversion of the labeled 18. [b] See Experimental Section.

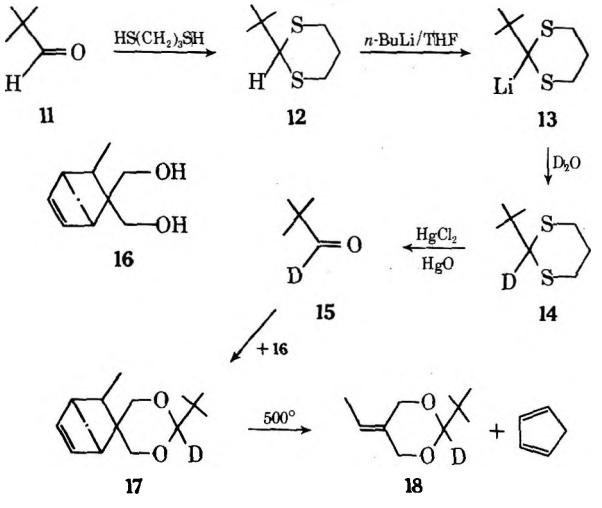
models of this conformation show that the migrating hydrogen atom is positioned 3 Å away from the migrating terminus. Indeed, cyclic acetals 8 also undergo thermal cleavage reaction but require higher temperatures.

In these cases, the cleavage reaction does not involve a fragmentation, but an isomerization of the acetals 8 to yield the corresponding acyclic esters 10. Therefore the pressure-increase technique we employed for acyclic acetals to follow the kinetics was not adequate.[3b]

These problems prompted us to undertake some experiments related more specifically with the hydrogen transfer itself, using both a 2-proteo- and a 2-deuterio-5-alkylidenedioxane 8.

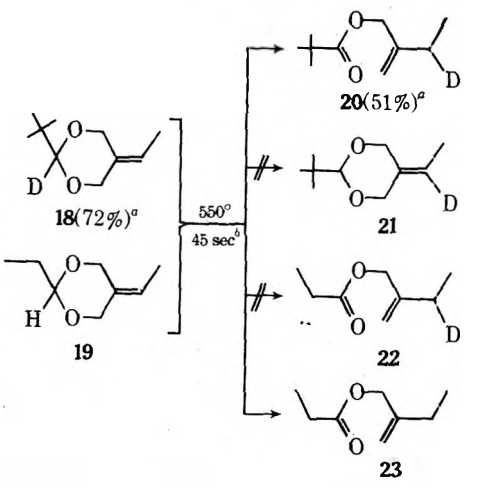
Synthesis of 2-*tert*-Butyl-5-ethylidenedioxane-2-*d*. The general procedure for the synthesis of 5-alkylidenedioxanes has been described by us previously.[7] In the present case, the key intermediate was pivalaldehyde-*1-d* (15), which was prepared by a sequence of deuterium incorporation steps as shown in Scheme I; the processes and the conditions were those of Seebach for the synthesis of benzaldehyde-*1-d*.[8] Condensation of 15 with diol 16 gave acetal 17, which was pyrolyzed at such a temperature that the retro-Diels–Alder reaction of 17 took place without causing the rearrangement of dioxane 18. The deuterium incorporation as measured by means of a nmr integration was 72% both in aldehyde 15 and dioxane 18.

Scheme I



Rearrangement of 5-Alkylidenedioxanes. First of all, our aim was to prove the intramolecular [1,5] shift of the hydrogen atom at the C-2 position in the isomerization of 8 to 10. For this purpose, we have chosen to examine the possibility of an isotope crossover in the thermolysis of a 1:1 mixture of deuterated dioxane 18 and an undeuterated analog, 2-ethyl-5-ethylidene-1,3-dioxane (19). The choice of dioxanes 18 and 19 is dictated by the requirement that the rates of isomerization of both compounds are comparable so that such an experiment is meaningful and valid. In Scheme II, conditions of the pyrolysis and results are summarized, from which a number of conclusions can be obtained.

Scheme II



[a] Deuterium incorporation in parentheses. [b] Conversion of the dioxanes: 75 ± 5%.

(1) The undeuterated dioxane 19 isomerizes exclusively to (2-methylene)butylpropionic acid ester (23) in which no deuterium is incorporated as shown by the nmr spectrum; in other words, compound 22 has not been found in the reaction mixtures.

(2) The deuterium in the products is found exclusively in the pivalate 20 and is specifically located at the C-3 position in the alkyl chain. Together with the above fact, the results indicate that each dioxane has undergone an intramolecular [1,5] hydrogen migration.

(3) The recovered dioxane 18 shows an nmr pattern for the ethylidene group identical with that of the starting material; no dioxane 21 has been detected in the reaction mixture. This fact suggests that the rearrangement is irreversible. This conclusion is to be expected since the $\Delta\Delta H°_{298}$ (dioxane 18–ester 20) is calculated[9] to be ~16 kcal/mol in favor of the ester, which, furthermore, possesses a higher entropy factor at 550°.

(4) The deuterium content of ester 20 amounts to only 51% while the percentage of deuterium in the recovered dioxane 18 rises to 94%. This enrichment reveals a significant first-order deuterium isotopic effect which is in agreement with the conclusion obtained so far.

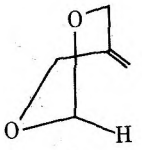
Deuterium Kinetic Isotopic Effect. In order to estimate the deuterium kinetic isotopic effect in the rearrangement, dioxane 18 with lower deuterium contents was pyrolyzed alone in the gas phase. From the experimental results, the deuterium kinetic isotopic effects k_H/k_D were calculated; they are summarized in Table I. The scatter in these values arises mainly from uncertainty in the conversion of the ratio of 18. The observed value of 3 ± 1 at 510° for k_H/k_D is in the range reported for other [1,5] hydrogen migrations having a highly symmetrical transition state,[10,11,12] although the large uncertainty precludes definite conclusions about the geometry of the transition state for the pyrolysis of 18.

Conclusion

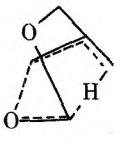
In summary, our observations on the thermal rearrangement of dioxanes of type 8 have shown that the reaction is intramolecular (lack of crossover), that it involves a specific [1,5] hydrogen shift with double-bond migration,[5,6] and that the hydrogen shift occurs in the slow reaction step.

These experimental data are characteristic for a concerted [1,5] sigmatropic reaction. Recent mechanistic proposals for the retro-ene reaction[13] have underlined the linear (coaxial) relationship of the hydrogen and the atoms between which it is transferred in the transition state. For 5-alkylidene-1,3-dioxanes, a bicyclic transition state 24,

arising from a boat conformation **9**, would be required. Such a structure is highly strained, but, in view of the large activation barrier involved in the reaction, the geometry of **24** may be attainable.



9



24

Experimental Section

The fractional distillation and the preparative glc techniques used are the same as earlier.[2] The infrared spectra were taken as liquid films. Nmr spectra were taken at 60 MHz in carbon tetrachloride with TMS as internal standard.

2-*tert*-Butyl-1,3-dithiane (12). The compound was prepared according to Seebach's general procedure.[8] Starting from 162 g (1.5 mol) of 1,3-propanedithiol and 129 g (1.5 mol) of pivalaldehyde there was obtained 167 g (64%) of distilled dithiane **12**: bp 115° (14 mm); n^{40}D 1.5305. The colorless liquid crystallized on standing: mp 37.5°; ir 2980, 2910, 1500, 1350, and 900 cm^{-1}; nmr 1 H singlet at δ 8.08, 9 H singlet at δ 2.27.

2-*tert*-Butyl-1,3-dithiane-*2-d* (14). was prepared according to Seebach's general procedure.[8] Starting from 156 g (0.89 mol) of **12**, 144 g (92%) of **14** was obtained, ir new bands at 1015, 1030, and 742 cm^{-1}. The nmr integration of the singlet at δ 8.08, when compared to the other signals, shows an isotopic mixture containing 72% of 2-*tert*-butyl-1,3-dithiane-*2-d* (**14**).

Pivalaldehyde-*1-d* (15). In a three-necked reaction vessel (thermometer, stirrer, and condenser), 144 g (0.82 mol) of dithiane **14**, 150 ml of water, 1200 ml of dioxane, 445 g of mercuric chloride, and 161 g of mercuric oxide[8] were heated to gentle boiling under nitrogen. The orange slurry turned white and the solution became green. After 4 hr the condenser was replaced by a distillation column. The distilling pivalaldehyde **15** was collected in a trap cooled to −5°. The collected mixture (76 g) contained the aldehyde and small amounts of water and dioxane. The distillate was washed twice with water and dried over calcium chloride to give aldehyde **15** (64 g), which still contained a trace of dioxane. The overall yield calculated from starting pivalaldehyde was 49.5%. The ir spectrum of **15** was similar to that of undeuterated aldehyde with additional bands at 2140, 2100, 1255, 1120, 1060, and 855 cm^{-1}. In the nmr spectrum, the integration of proton H-1 at δ 9.4 was compared to that of the *tert*-butyl protons at δ 1.17 and showed an isotopic content of 70–75% of pivalaldehyde-*1-d* (**15**).

2-*tert*-Butyl-5-ethylidene-1,3-dioxane-2-*d* (18). The acetal formation and the procedure of retrodienic pyrolysis have been described previously.[7] The nmr spectra of the undeuterated species **18** have also been described.[4] Integrations of the signals between δ 3.75 and 4.18 (3 protons OCH_2 plus H-2 protons) and the signal of the singlet at δ 0.92 (9 *tert*-butyl protons) showed that the isotopic mixture **18** contains 72% of dioxane-*2-d*.

Thermal Isomerization of Dioxane 18. The pyrolysis technique, the synthesis, and data of compounds **19** and **23** have been described elsewhere.[2] The isotopic mixtures **18** with different deuterium contents were obtained by mixing the deuterated **18** (deuterium content 72%) with undeuterated **18**. The conversions were calculated after calibration of the glc chromatograms with pure samples of dioxanes and esters on two different columns (SE-30 and Reoplex on Chromosorb W-HMDS). The isotopic effect has been calculated as follows.

Let a_sH, a_rH and a_sD, a_rD be the concentrations of the starting and recovered proteo and deuterio dioxanes, respectively. The measured total conversion X relates these quantities as follows.

$$a_r\mathrm{H} + a_r\mathrm{D} = (1 - X)(a_s\mathrm{H} + a_s\mathrm{D}) \quad (1)$$

The kinetic isotope effect is given by eq 2.[14]

$$\frac{k_H}{k_D} = \frac{\log(a_r\mathrm{H}/a_s\mathrm{H})}{\log(a_r\mathrm{D}/a_s\mathrm{D})} \quad (2)$$

The measured deuterium contents D_s and D_r (Table I) are related to the ratio of the starting and recovered deuterio and proteo dioxanes in the following way.

$$\frac{D_s}{100 - D_s} = \frac{a_s\mathrm{D}}{a_s\mathrm{H}} = i_s \quad (3)$$

$$\frac{D_r}{100 - D_r} = \frac{a_r\mathrm{D}}{a_r\mathrm{H}} = i_r \quad (4)$$

By replacing the parameters in eq 1 with their equivalent values in eq 3 and 4, the following relations are obtained.

$$\frac{a_r\mathrm{H}}{a_s\mathrm{H}} = (1 - X)\,\frac{1 + i_s}{1 + i_r} \quad (5)$$

$$\frac{a_r\mathrm{D}}{a_s\mathrm{D}} = (1 - X)\,\frac{1 + 1/i_s}{1 + 1/i_r} \quad (6)$$

Thus k_H/k_D in eq 2 can be computed from the experimental data X, D_s, and D_r.

2-Methylenebutyl-*3-d*-pivalic Acid Ester (20). The ir was similar to that of the undeuterated butyl ester with additional bands at 2300, 2100, 1015, and 815 cm^{-1}. The deuterium amount is calculated by nmr; the integration of the CH_2 quartet of the butyl group at δ 2.1 is compared to that of the OCH_2 at δ 4.48 or the methylene at δ 4.92.

Acknowledgment. We thank Professor Y. L. Chow for many constructive discussions.

Registry No. 12, 6007-21-2; **14,** 49810-98-2; **15,** 41162-98-5; **18,** 49811-00-9; 1,3-propanedithiol, 109-80-8; pivalaldehyde, 630-19-3.

References and Notes

(1) Laboratoire Associé au Centre National de la Recherche Scientifique, No. 135.
(2) F. Mutterer, J. M. Morgen, J. M. Biedermann, F. Weiss, and J. P. Fleury, *Tetrahedron*, **26,** 477 (1970).
(3) (a) H. M. R. Hoffmann, *Angew. Chem.*, **81,** 597 (1969); (b) F. Mutterer, P. Baumgartner, and J. P. Fleury, *Bull. Soc. Chim. Fr.*, 1528 (1970).
(4) P. DeSaulles and J. P. Fleury, *Org. Magn. Resonance*, **2,** 245 (1970).
(5) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, p 599.
(6) P. de Mayo, "Molecular Rearrangements," Vol. I, Interscience New York, N. Y., 1963, p 30.
(7) F. Mutterer, J. M. Morgen, J. M. Biedermann, J. P. Fleury, and F. Weiss *Bull. Soc. Chim. Fr.*, 4478 (1969).
(8) D. Seebach, B. W. Erickson, and G. Singh, *J. Org. Chem.*, **31,** 4304 (1966).
(9) D. R. Stall, E. F. Westrune, and G. C. Sinke, "The Chemical Thermodynamics of Organic Compounds," Wiley, New York, N. Y., 1969.
(10) W. R. Roth and J. Konig, *Justus Liebigs Ann. Chem.*, **699,** 24 (1966).
(11) H. Kloosterziel and A. P. ter Borg, *Recl. Trav. Chim. Pays-Bas*, **84,** 1305 (1965).
(12) C. H. de Puy and R. W. King, *Chem. Rev.*, **60,** 431 (1960).
(13) H. Kwart and J. Slutsky, *Chem. Commun.*, 1182 (1972).
(14) L. Melander, "Isotope Effects on Reaction Rates," Ronald Press, New York, N. Y., 1960.

Nucleophilic Displacements on Halogen Atoms. III. Reduction of α,α-Dichlorobenzyl Benzyl Sulfoxide to α-Chlorobenzyl Benzyl Sulfoxides

Bruce B. Jarvis* and Mary M. Evans[1]

Department of Chemistry, University of Maryland, College Park, Maryland 20742

Received October 17, 1973

Attempted dichlorination (with SO_2Cl_2) of the α-carbon atom of either dibenzyl sulfoxide or benzyl phenyl sulfoxide led only to cleavage of the carbon–sulfur bond. Dibenzyl sulfide could be dichlorinated at the α position, but treatment of benzyl phenyl sulfide with 2 equiv of SO_2Cl_2 gave carbon–sulfur bond cleavage. Several α,α-dichlorobenzyl benzyl sulfoxides were made from the corresponding sulfides by oxidation with peracid. Reduction of α,α-dichlorobenzyl benzyl sulfoxide (**2a**) to a mixture of diastereomeric α-chlorobenzyl benzyl sulfoxides was carried by (a) $(Me_2N)_3P$ in aqueous solvents and (b) chromous ion in aqueous solvents. Variations in the ratios of diastereomers obtained were studied as a function of solvent and reducing agent. Little variation in product ratios was observed with $(Me_2N)_3P$ but product ratios in the reduction of **2a** with chromous ion varied a great deal.

In the past few years, a number of reports dealing with α-halo sulfoxides have appeared. Up until recently, these compounds were relatively unknown; now there exist a number of methods for their synthesis.[2] Since the sulfinyl group is capable of asymmetry, many of these α-halo sulfoxides [*e.g.*, $R^1R^2CXS(O)R^3$] are diastereomeric (and/or optically active) and therefore an added structural feature is naturally present.

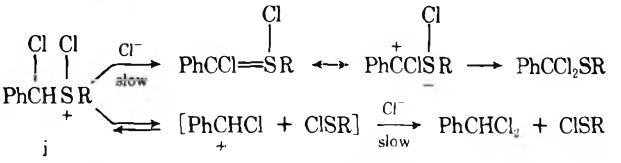
A number of workers have observed that α-chlorination of sulfoxides may stereoselectively lead to one of two possible diastereomeric α-chloro sulfoxides.[2c,f,g,i,j,3] Furthermore, α-chlorination of sulfides followed by oxidation also may give α-chloro sulfoxides with a high degree of stereoselectivity.[2m] We sought an alternate and perhaps complementary synthetic pathway to the stereoselective synthesis of α-chloro sulfoxides based on reductions of α,α-dichloro sulfoxides. Analogy for such a reaction can be found in the reductions of α-halo sulfones.[4]

Results and Discussion

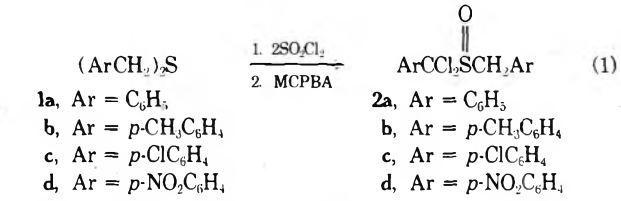
We tried two principal routes into α,α-dichloro sulfoxides: dichlorination of sulfoxides and dichlorination of sulfides followed by oxidation to the desired sulfoxides. Of these methods, only the latter was successful.

Initially, we attempted to synthesize α,α-dichlorobenzyl phenyl sulfoxide. However, attempted dichlorination of either benzyl phenyl sulfide or benzyl phenyl sulfoxide by the usual procedures[5] led only to cleavage of the benzylic carbon–sulfur bond. Monochlorination of either benzyl phenyl sulfide or benzyl phenyl sulfoxide to give the corresponding α-chlorination products proceeds in high yields. However, treatment of these α-chloro sulfides or sulfoxides with an additional 1 equiv of chlorinating agent (*e.g.*, sulfuryl chloride) under a variety of conditions invariably led to cleavage products (benzal chloride) and no α,α-dichlorobenzyl phenyl sulfide or α,α-dichlorobenzyl phenyl sulfoxide were observed. It appears that one of the driving forces for cleavage of the carbon–sulfur bond is the increased stability of the benzylic cation possessing an α-chlorine atom.[6] As evidence of this, dichlorination of *p*-nitrobenzyl phenyl sulfide and *p*-cyanobenzyl phenyl sulfide (but not the corresponding sulfoxides) followed by oxidation with *m*-chloroperbenzoic acid (MCPBA) led to the *p*-nitro-α,α-dichlorobenzyl phenyl sulfoxide and *p*-cyano-α,α-dichlorobenzyl phenyl sulfoxide, respectively, in good yields. Unfortunately, these compounds were extremely difficult to handle owing to their sensitivity to moisture and protic solvents. The chemistry of these sulfoxides will be the subject of a separate article.

The proposed mechanism for α-chlorination of sulfides[5b] suggests that cleavage products and α-chloro sulfides result from competitive second-order reactions of the intermediate chlorosulfonium ions (i) with chloride ion. The scheme we propose combines certain ideas previously presented.[5] This scheme explains why cleavage becomes more favored when an α-chlorine atom is already present, since the resulting carbonium ion will be more stable.[6] Nucleophilic displacement on the α-carbon atom in i by Cl^- [5b] seems less likely since the α-chlorine atom should retard the S_N2 reaction.[7]



The aryl-substituted dibenzyl sulfides (**1**) could be dichlorinated and oxidized to the α,α-dichlorobenzyl benzyl sulfoxide (**2**) in good yields (eq 1). Little carbon–sulfur



1a, Ar = C_6H_5	**2a**, Ar = C_6H_5
b, Ar = *p*-$CH_3C_6H_4$	**b**, Ar = *p*-$CH_3C_6H_4$
c, Ar = *p*-ClC_6H_4	**c**, Ar = *p*-ClC_6H_4
d, Ar = *p*-$NO_2C_6H_4$	**d**, Ar = *p*-$NO_2C_6H_4$

(1)

bond cleavage was observed in this system in contrast to benzyl phenyl sulfide (*vide supra*). This in part may be due to the instability of benzylsulfenyl chloride (which would be formed on cleavage) compared to benzenesulfenyl chloride.[8] Although the basis for this instability of alkylsulfenyl chlorides (*cf.* arylsulfenyl chlorides) is kinetic in nature, their thermodynamic stabilities may well parallel the kinetic stabilities.[8] Attempted chlorination (with SO_2Cl_2) of α-chlorobenzyl benzyl sulfoxide to give the known[9] dichloro sulfoxide **2a** instead gave a mixture of at least five different products (benzal chloride was a major constituent), none of which was **2a**. Such behavior is not surprising in view of the ease with which chlorination of sulfoxides can lead to carbon–sulfur bond cleavage in the cases where relatively stable carbonium ions ($PhCHCl^+$ in this case) can be formed.[10]

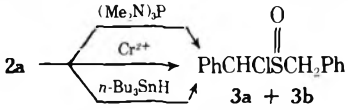
A study was made of the reduction of the dichloro sulfoxide **2a** to the monochloro sulfoxides **3a** and **3b** with several reducing agents: hexamethylphosphorous triamide [$(Me_2N)_3P$], chromous chloride, and tri-*n*-butyltin hydride. Tri-*n*-butyltin hydride was used only in one experiment. Owing to the thermal instability of **2a**, the reaction was carried out below room temperature under uv irradiation. The reaction proved to be slow even with 1 *M* tri-*n*-butyltin hydride in tetrahydrofuran (THF), and work-up

Table I
Reduction of Benzyl α,α-Dichlorobenzyl Sulfoxide (2a) with Hexamethylphosphorous Triamide [$(Me_2N)_3P$] at 25° [a]

Aqueous solvent	[3a/3b] ± 5%	Aqueous solvent	[3a/3b] ± 5%
100% EtOH	1.00	70% Dioxane	0.83
100% t-BuOH	*0.71*	*46% Dioxane*	*0.67*
90% DMF	0.48	90% EtOH	0.69
90% HMPT	0.65	80% EtOH	0.77
90% THF	1.00	100% EtOH[b]	1.00
90% Dioxane	0.77	90% THF[b]	0.91
80% DMF	0.59	90% HMPT[b]	1.40
70% DMF	0.67	90% DMF[b]	1.11
80% Dioxane	0.77		

[a] Within experimental error these ratios showed no changes over the temperature range of 25–65°. [b] 1.0 *M* in $LiClO_4$.

was complicated by the presence of unreacted tri-*n*-butyltin hydride and tri-*n*-butyltin chloride. However, the reduction of **2a** under these conditions did proceed to give *ca.* a 70% yield of **3a** and **3b** in a ratio of 3:1, respectively.



(2)

The chloro sulfoxides **3a** and **3b** have been reported previously (although their configurations have not been assigned) and have the following physical properties: **3a**, mp 113–113.5°, nmr ($CDCl_3$) signal at δ 5.22 for the methine proton,[2m] **3b**, mp 117–118.5°, nmr ($CDCl_3$) signal at δ 5.45 for the methine proton.[2j]

The reaction of **1a** with $(Me_2N)_3P$ was run under a variety of conditions in hopes of realizing a large variation in the product ratio, **3a:3b**. However, employing a large number of different solvent and reaction temperature conditions had little marked effect on the product ratios. Under the conditions employed (see Table I), the ratios of **3a:3b** varied from *ca.* 0.5 to 1.4.

The effect of added lithium perchlorate was negligible in 90% ethanol and 90% THF solvents, but the salt appeared to cause a significant change in the product ratios in the dipolar aprotic solvents dimethylformamide (DMF) and hexamethylphosphoric triamide (HMPT) (Table I).

The pathway for reduction of **2a** by $(Me_2N)_3P$ appears closely related to analogous reductions observed in the reactions of δ-halo sulfones with triphenylphosphine[4,11] and in the debromination of bis(α-bromobenzyl) sulfoxide with $(Me_2N)_3P$ to give diphenylthiirane 1-oxide and $(Me_2N)_3PBr_2$.[13] These reactions involve intermediate carbanions which can undergo portonation (leading to reduction products[4,12]) or lose halide ion.[13]

The α-sulfinyl carbanion has been of keen interest lately both from a theoretical[14] and experimental[15] standpoint. At the initiation of this work, we felt that a solvent study such as that described above would lead to more insight into the nature of the α-sulfinyl carbanion. However, it is now clear that the stereochemical fate of the α-sulfinyl carbanion is solvent dependent[16] and that the small variation we observe (Table I) in the product ratios can easily be accounted for in terms of asymmetric solvation of the intermediate carbanions.[17]

A more interesting result was obtained in the chromous ion (Cr^{2+}) reductions of **2a** to give **3a** and **3b** (Table II). The reaction of Cr^{2+} with **2a** in aqueous solvents appeared to take place instantly. The monochloro sulfoxides **3a** and **3b** could be further reduced to dibenzyl sulfoxide, although at a rate significantly slower than that observed for the reduction of **2a**. The monochloro sulfoxides **3a** and **3b** did not undergo reduction by Cr^{2+} at the same rates; so care was taken to ensure that reduction of **2a** proceeded only as far as to give the monochloro sulfoxides **3a** and **3b**.

Table II
Reduction of Benzyl α,α-Dichlorobenzyl Sulfoxide (2a) with $CrCl_2$ at 25°

Aqueous solvent	[3a/3b] ± 5% [a]	Aqueous solvent	[3a/3b] 5% [a]
90% EtOH	38	90% DMSO	1.0
80% EtOH	66	90% HMPT	5.4
90% MeOH	*32*	90% DMF	2.5
90% THF	30	80% DMF	6.3
90% Dioxane	30	70% DMF	12
80% Dioxane	48		

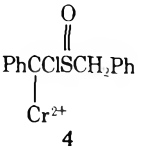
[a] Within experimental error, these ratios showed no change over the temperature range of 25–65°. Added lithium perchlorate (up to 2 *M*) also had no apparent effect on these ratios in 90% DMF, 90% dioxane, and 90% ethanol solutions.

It is clear from Table II that the **3a/3b** ratio varies significantly with solvent conditions. In particular, use of 90% aqueous dipolar aprotic solvents (DMSO, DMF, and HMPT) gave **3a/3b** ratios of *ca.* 1–5 whereas 90% aqueous ether and alcohol solvents gave **3a/3b** ratios of *ca.* 30. Furthermore, increasing the per cent of water in all solutions led to a marked increase in the **3a/3b** ratio. Again the product ratios showed essentially no change over a 40° temperature range or any change upon added lithium perchlorate.

A number of studies have been made on the reduction of alkyl halides with chromous ion.[18] These reactions are believed to involve several steps: a slow abstraction of a chlorine atom (in RCl) by Cr^{2+} to give $[CrCl]^{2+}$ + R·, followed by a rapid coupling of R· with another Cr^{2+} to give $[RCr]^{2+}$, and finally a slow protonolysis of the C–Cr bond to give RH + Cr^{3+}. This last step occurs with retention of configuration[19] and can be followed spectrophotometrically.[20]

We briefly examined the question of whether we observed the intermediate **4** in the reaction of **2a** with Cr^{2+} and found that on mixing of a solution of **2a** with Cr^{2+}, an appreciable absorbance was observed at 365 nm. The absorbance decreased with time, and a plot of log $(A - A_\infty)$ *vs.* time gave a linear plot, indicating that first-order kinetics was being observed. This observation is consistent with results from kinetic studies of similar reactions.[23]

The product-determining step in the reaction of **2a** with Cr^{2+} would appear to be the coupling of the benzylic radical $PhCClS(O)CH_2Ph$ with a chromous ion[18,21] to give **4** (actually a set of diastereomers). It seems unlikely that the change in solvent has an appreciable effect on the conformation of the intermediate radical. However, the chemical nature of chromous ion probably is sensitive to solvation effects,[21,22] and therefore a change in solvent is likely to lead to a significant change in reactivity.



4

Experimental Section

Melting points were taken on a Mel-Temp apparatus and are uncorrected. The nmr spectra were recorded on a Varian Associates A-60D nmr spectrometer at ambient temperatures. The spectra were taken in deuteriochloroform with tetramethylsilane (δ 0.00) as an internal standard. The ir spectra of the isolated compounds were taken in KBr pellets; those spectra of solutions were taken in carbon tetrachloride solutions. Elemental analyses were performed by Dr. Franz Kasler and Mrs. Shelesa Brew at the Department of Chemistry, University of Maryland.

Attempted Syntheses of α,α-Dichlorobenzyl Phenyl Sulfoxide. To a solution of 1 g (5.0 mmol) of benzyl phenyl sulfide in 10 ml of carbon tetrachloride was added dropwise (at room temperature) 1.5 g (11 mmol) of sulfuryl chloride in 2 ml of carbon tetrachloride. The course of the reaction was monitored by nmr spectroscopy, which showed that the benzyl phenyl sulfide was smoothly converted by the first equivalent of sulfuryl chloride to α-chlorobenzyl phenyl sulfide. An nmr spectrum of the reaction mixture taken after all the sulfuryl chloride solution had been added showed that a significant amount of benzal chloride (benzylic proton located at δ 6.6) and a smaller amount of benzyl chloride (benzylic proton located at δ 4.5) had been formed. The carbon tetrachloride was removed by rotary evaporation and the oil was dissolved in 10 ml of dry methylene chloride. To this mixture was added 1.0 g (5.0 mmol) of *m*-chloroperoxybenzoic acid (MCPBA). The reaction mixture was stirred for 10 min and then washed with dilute sodium bicarbonate. The solution was dried ($MgSO_4$) and the solvent was removed by rotary evaporation. An ir spectrum showed the absence of any appreciable absorption in the region of 1050–1100 cm^{-1}, where the S–O stretching frequency for sulfoxides is found.[23] Variations in reaction times and temperatures as well as solvents (DMF, methylene chloride, and sulfolane were used) still led to no observable amount of α,α-dichlorobenzyl phenyl sulfoxide.

Attempts to chlorinate α-chlorobenzyl phenyl sulfoxide[2f] (which can be made in nearly quantitative yield by the monochlorination of benzyl phenyl sulfoxide) with sulfuryl chloride and pyridine[2g] in several solvents (DMF, methylene chloride, and sulfolane) gave only cleavage products[24] and recovered starting material.

α-Chlorination of Benzyl Phenyl Sulfides Containing Electron-Withdrawing Groups. To a solution of 1.0 g (4.1 mmol) of 4-nitrobenzyl phenyl sulfide[25] dissolved in 20 ml of dry carbon tetrachloride was added dropwise 1.34 g (9.9 mmol) of sulfuryl chloride in 5 ml of carbon tetrachloride. After 30 min, the carbon tetrachloride was removed by rotary evaporation and the oil was taken up in 20 ml of dry methylene chloride. To this solution was added, in increments of *ca.* 0.2 g, 0.81 g (4.0 mmol) of 85% MCPBA. After 5 min, the reaction mixture was washed with water and 10% sodium bicarbonate solution. The organic layer was dried ($MgSO_4$) and the solvent was removed by rotary evaporation. On standing, the oil (1 g) solidified, mp 82–91°. An ir spectrum of this material showed a sulfoxide band at 1105 cm^{-1} and no carbonyl band; tlc on alumina showed one major and several minor spots. Attempts to recrystallize this material from Skellysolve B–methylene chloride led to considerable decomposition of the material. When this material was heated in absolute methanol for a few minutes, methyl 4-nitrobenzoate, mp 94.0–94.5 (lit.[26] mp 96°), was isolated when the solution was cooled. Similar results were obtained when these procedures were attempted with 4-cyanobenzyl phenyl sulfide.

Benzyl α,α-Dichlorobenzyl Sulfoxide (2a). Dibenzyl sulfide (5.0 g, 23 mmol) was dissolved in 20 ml of dry carbon tetrachloride. To this solution was added, dropwise, over a 1-hr period, 6.5 g (48 mmol) of sulfuryl chloride in 15 ml of dry carbon tetrachloride. After the reaction mixture had stirred for an additional 1 hr, the solvent was removed by rotary evaporation. To the resulting oil were added 40 ml of dry methylene chloride and, in increments, 4.7 g (23 mmol) of 85% MCPBA. Five minutes later, the reaction mixture was washed with two portions of a saturated sodium carbonate solution and dried ($MgSO_4$). Rotary evaporation of the solvent yielded an oil which solidified upon cooling to 0°. This solid was collected, washed with pentane, and recrystallized from methylene chloride–Skellysolve B to give 5.0 g (72%) of **2a**, mp 87.0–88.0° (lit.[9] mp 86.6–89.5°).

α,α-Dichloro-4-Methylbenzyl 4-Methylbenzyl Sulfoxide (2b). In a fashion similar to the procedure given for the preparation of **2a**, 2.0 g (8.2 mmol) of bis(4-methylbenzyl) sulfide[27] was treated first with 2.3 g (17.0 mmol) of sulfuryl chloride and then with 1.65 g (8.1 mmol) of 85% MCPBA. The crude product was recrystallized from methylene chloride–Skellysolve B to give 1.5 g (56%) of the product **2b**: mp 106.0–107.0°; nmr δ 2.32 (s, 3 H), 2.42 (s, 3 H), 3.42 (d, 1 H), 4.10 (d, 1 H, J = 13 Hz), 7.0–7.7 (m, 8 H); ir 1086 cm^{-1} (SO).

Anal. Calcd for $C_{16}H_{16}Cl_2OS$: C, 58.71; H, 4.95. Found: C, 58.52; H, 4.98.

4-Chlorobenzyl α,α-4-Trichlorobenzyl Sulfoxide (2c). In a fashion similar to the procedure given for the preparation of **2a**, 5.0 g (18 mmol) of bis(4-chlorobenzyl) sulfide[27] was treated first with 4.9 g (36 mmol) of sulfuryl chloride and then with 3.6 g (18 mmol) of 85% MCPBA. The crude product was recrystallized from methylene chloride–Skellysolve B to give 4.1 g (63%) of **2c**: mp 106.5–107.0°; nmr δ 3.42 (d, 1 H), 4.16 (d, 1 H, J = 13 Hz), 7.1–7.9 (m, 8 H); ir 1087 cm^{-1} (SO).

Anal. Calcd for $C_{14}H_{10}Cl_4OS$: C, 45.68; H, 2.74. Found: C, 45.41; H, 2.70.

α,α-Dichloro-4-nitrobenzyl 4-Nitrobenzyl Sulfoxide (2d). Bis(4-nitrobenzyl) sulfide[27] (2.00 g, 6.6 mmol) was dissolved in 50 ml of dry methylene chloride. To this solution was added, dropwise, over a 30-min period, 1.84 g (13.6 mmol) of sulfuryl chloride in 8 ml of dry methylene chloride. Four hours later, the solvent was removed by rotary evaporation. To the resulting oil were added 20 ml of dry methylene chloride and, in increments, 1.34 g (6.6 mmol) of 85% MCPBA. Five minutes later, the reaction mixture was washed with two portions of a saturated sodium carbonate solution and dried ($MgSO_4$). Rotary evaporation of the solvent yielded an oil which solidified upon cooling to 0°. This solid was collected, washed with pentene, and recrystallized from methylene chloride–Skellysolve B. The yield of **2d** was 1.75 g (68%): mp 123.0–124.0; nmr δ 3.33 (d, 1 H), 4.07 (d, 1 H, J = 13 Hz), 6.9–8.0 (m, 8 H); ir 1510 (NO_2) and 1100 cm^{-1} (SO).

Anal. Calcd for $C_{14}H_{10}Cl_2N_2O_5S$: C, 43.20; H, 2.59. Found: C, 43.12; H, 2.64.

Treatment of Dibenzyl Sulfoxide with 2 Equiv of Sulfuryl Chloride in the Presence of Pyridine. In 20 ml of dry methylene chloride was dissolved 3.0 g (13.0 mmol) of dibenzyl sulfoxide, and the solution was cooled to 0°. To this solution were added 4.05 g (51.2 mmol) of pyridine and, over a period of 1 hr, 3.46 g (25.6 mmol) of sulfuryl chloride in 8 ml of dry methylene chloride. Thirty minutes later, the solution was washed with a dilute hydrochloric acid solution and a dilute sodium thiosulfate solution and dried ($MgSO_4$). The solvent was removed by rotary evaporation. The nmr spectrum of the resulting oil contained, in addition to the aromatic region (δ 7.1–8.2), a singlet at δ 6.6, corresponding to benzal chloride, and a multiplet between δ 3.6 and 4.7. The range of the latter multiplet ruled out the possibility of the presence of the α,α-dichloro sulfoxide **2a** and both of the diastereomers of the α-chloro sulfoxide **3a** and **3b**. Tlc (50% ether–50% Skelly B) showed that five compounds were present. Nothing further was done with this mixture.

Dibenzyl sulfide (5 g, 23.3 mmol) was dissolved in 20 ml of dry carbon tetrachloride. To this solution was added, dropwise, 3.14 g (23.3 mmol) of sulfuryl chloride in 8 ml of dry carbon tetrachloride. After 30 min, the carbon tetrachloride was removed by rotary evaporation. To the resulting oil were added 25 ml of dry methylene chloride and then, in increments, 4.73 g (23.3 mmol) of 85% MCPBA. Ten minutes later the reaction mixture was washed with a saturated sodium carbonate solution and dried ($MgSO_4$). A solid remained after rotary evaporation of the solvent. This was shown by its nmr spectrum to be benzyl α-chlorobenzyl sulfoxide (5.3 g, 86%); the two diastereomers **3a** and **3b** were formed in a 1:1 ratio. Repeated recrystallization of this mixture from carbon tetrachloride–Skellysolve B led to the isolation of the pure diastereomer **3a**, mp 113.0–113.5° (lit.[2m] mp 112–113°).

The supernatants from the recrystallizations described above were combined, and out of the resulting solution was isolated the other diastereomer **3b**, which had mp 117.0–118.5° (lit.[2j] mp 118.0–118.5°).

Reduction of Benzyl α,α-Dichlorobenzyl Sulfoxide (2a) with Hexamethylphosphorous Triamide. General Procedure. The sulfoxide **2a** (0.25 g, 0.84 mmol) was dissolved in 4.0 ml of the chosen solvent. Reagent-grade solvents were used in every case. The following solvents were further purified: dioxane (distillation from sodium), THF (distillation from lithium aluminum hydride), DMSO (vacuum distillation from calcium hydride), and HMPT (vacuum distillation from calcium hydride). To the solution were added 0.1 g (1.0 mmol) of triethylamine and 0.14 g (0.84 mmol) of hexamethylphosphorous triamide. After the reaction mixture had stirred for 15 min, it was poured into 20 ml of water, and the products were extracted with three 15-ml portions of ether. The combined ethereal extracts were washed with four 15-ml portions of water and were dried ($MgSO_4$); the solvent was removed by rotary evaporation. An nmr spectrum was taken of the mixture, and the ratio of the area of the peaks caused by the methine protons of **3a** and **3b** was determined. The monochloro sulfoxides **3a** and **3b** were isolated either by crystallization or chromatography and identified by melting point, mixture melting point, and spectroscopy (ir and nmr).

Salt Effect Study. In these experiments 0.42 g of anhydrous lithium perchlorate was added to the reaction mixture, making the solution 1 *M* with respect to the salt.

Temperature Study. The above procedure was followed except

that the reaction mixture was held at the specified temperature (45 or 65°) for the 15-min reaction period.

Test for Epimerization of Benzyl α-Chlorobenzyl Sulfoxide under Conditions of the Reduction. In 10% Water–90% THF. To approximate the reaction conditions as closely as possible, it was assumed that a reduction had proceeded to 50% completion and that the phosphine and the monochloro sulfoxide were, therefore, present in equal concentration. To 13.5 ml of THF were added 0.40 g of benzyl α-chlorobenzyl sulfoxide (**3a**), **3b** (1.5 mmol), 0.3 g (3.0 mmol of triethylamine, 1.5 ml (1.5 mmol) of a 1.0 *M* hydrochloric acid solution, and 0.24 g (15 mmol) of hexamethylphosphorous triamide. Portions of 4.5 ml of this solution were withdrawn after 15 min, 1 hr, and 3 hr; each aliquot was worked up as outlined in the General Procedure above. Initially the ratio was 1:>99; *i.e.*, diastereomer **3b** was not detectable. This ratio was not observed to change during the 3-hr period.

In 10% Water–90% DMF. The above procedure was repeated with DMF substituted for THF. After 15 min, the ratio of **3b** to **3a** was 1:94; after 1 hr, the ratio was 1:81; after 3 hr, it was 1:38.

Under these conditions, no reduction of benzyl α-chlorobenzyl sulfoxide occurred.

Test for Mass Loss during the Reduction. In 10% Water–90% THF. The sulfoxide **2a** (0.50 g, 1.68 mmol) was dissolved in 8.0 ml of a 10% water–90% THF solution. To this solution was added 0.1 g of acetophenone as an internal standard. Four milliliters of the solution was withdrawn and worked up as described in the General Procedure. A pmr spectrum showed the ratio of the area of the peaks caused by the methylene protons of sulfoxide **2a** to the area of the methyl singlet of acetophenone to be 1.7:1.0. To the remaining solution were added 0.1 g (1.0 mmol) of triethylamine and 0.14 g (0.84 mmol) of hexamethylphosphorous triamide. One hour later, this solution was worked up as usual. The ratio of the total area of the peaks caused by the methylene protons of **2a**, **3a**, and **3b** to the area of the methyl singlet of acetophenone was 1.5:1.0.

Reduction of Benzyl α,α-Dichlorobenzyl Sulfoxide (2a) with Triphenylphosphine. To a solution of 0.5 g (1.68 mmol) of sulfoxide **2a** in 25 ml of methanol was added 0.2 g (2.0 mmol) of triethylamine and 0.52 g (2.0 mmol) of triphenylphosphine. The reaction mixture was held at reflux (65°) for 24 hr; at that time tlc (70% ether–30% Skellysolve B) indicated that all of the starting material had been reduced. The reaction mixture was poured into 20 ml of water, and the products were extracted with two 20-ml portions of methylene chloride; the organic portions were dried ($MgSO_4$), and the solvent was removed by rotary evaporation. An nmr spectrum of the resulting oil indicated that the two α-chloro sulfoxides **3a** and **3b** were formed in equal amounts in a clean reaction. Under these same conditions, hexamethylphosphorous triamide reacted with **2a** in less than 1 min to give **3a** and **3b** in the same ratio.

Reduction of 2a with Tri-*n*-butyltin Hydride. To 0.25 g (0.84 mmol) of the sulfoxide **2a** dissolved in 1.5 ml of THF was added 0.50 g (1.74 mmol) of tri-*n*-butyltin hydride. Nitrogen was flushed through the system, and the temperature of the solution was kept between 0 and 25° as the reaction flask was irradiated with uv light for 4 hr. Tlc (70% ether–30% Skellysolve B) at that time indicated that nearly all of the starting material had been reduced. The THF was removed by rotary evaporation. An nmr spectrum of the resulting solution showed that the diastereomers **3a** and **3b** had been formed in the ratio 3:1. The sulfoxides **3a** and **3b** were isolated by chromatography (silica gel, 10% ether–Skellysolve B eluent) in 70% yield.

Reduction of 2a with Chromous Ion. General Procedure. All reductions were carried out in a manner analogous to this one example. To 9 ml of THF in a three-necked flask was added 0.3 ml of water. (If a 20% water–80% THF solution were needed, 1.3 ml of water would be added to 8 ml of THF. Similar adjustments were made for other solvent systems.) In another flask was dissolved 0.25 g (0.84 mmol) of the sulfoxide **2a** in 2 ml of a solution of 10% water–90% THF. Nitrogen was bubbled through both solutions for 5 min. Into the first solution were injected through a septum 0.7 ml (1.4 mmol) of a 2 *M* aqueous solution of chromium(II) chloride and then, as rapidly as possible, the sulfoxide solution. The reaction mixture was immediately poured into 20 ml of water, and the products were extracted with three 15-ml portions of ether. The combined ethereal extracts were washed with four 15-ml portions of water and were dried ($MgSO_4$). After the solvent had been removed by rotary evaporation, an nmr spectrum was taken of the crude reaction mixture, and the ratio of the areas of the peaks caused by the methine protons of **3a** and **3b** was determined.

Salt Effect Study. The above procedure was followed with the following addition. To the chromium(II) chloride solution was added 1.06 g of anhydrous lithium perchlorate, and to the sulfoxide solution was added 0.21 g of anhydrous lithium perchlorate, making both solutions 1 *M* with respect to the salt. These amounts of lithium perchlorate were doubled when a 2 *M* solution was used.

Temperature Study. The above procedure was followed except that both solutions were heated to the specified temperature (45 or 65°) before they were mixed together.

Dilution Study. In this case, the volume of the chromium(II) chloride solution was increased to 60 ml. The sulfoxide was dissolved in 2 ml of the solvent as before.

Reduction of Benzyl α-Chlorobenzyl Sulfoxide (3) with Chromium(II) Chloride. As described in the General Procedure above, 0.28 g (1.1 mmol) of a mixture of the diastereomers **3a** and **3b** was treated with 0.4 mmol of chromium(II) chloride. The initial ratio of the two isomers was 0.83:1.0. After the reduction, the α-chloro sulfoxides which remained (**3a** and **3b**) were in the ratio of 1.0:1.0.

Treatment of 2a with Potassium Thiophenoxide. To 0.25 g (0.84 mmol) of sulfoxide **2a** dissolved in 15 ml of absolute ethanol was added 0.25 g (1.68 mmol) of potassium thiophenoxide. The reaction mixture was heated to 60° for 2 hr. It was then poured into 20 ml of water, and the product was extracted with three 15-ml portions of ether. The combined ethereal extracts were washed with water and dried ($MgSO_4$). The solvent was removed by rotary evaporation. A pmr spectrum of the crude product showed that a considerable amount of starting material was present; no peaks occurred between δ 5 and 6, indicating that none of the reduced compound **3** had been formed. (Compounds **3a** and **3b** were stable under these conditions.) Similar results were obtained in 90% aqueous DMF solvent at 25°.

Registry No.—**1a**, 538-74-9; **1b**, 13250-88-9; **1c**, 23566-23-6; **1d**, 1835-71-8; **2a**, 30505-98-7; **2b**, 50323-83-6; **2c**, 50323-84-7; **2d**, 50323-85-8; dibenzyl sulfoxide, 621-08-9.

References and Notes

(1) National Science Foundation Trainee, 1969–1971.

(2) (a) C. G. Venier, H. H. Hsieh, and H. J. Barager, III, *J. Org. Chem.*, **38**, 17 (1973); (b) C. G. Venier and H. J. Barager, III, *J. Chem. Soc., Chem. Commun.*, 319 (1973); (c) M. Cinquini and S. Colonna, *J. Chem. Soc., Perkin Trans. 1*, 1883 (1972); (d) M. Cinquini, S. Colonna, and D. Landini, *J. Chem. Soc., Perkin Trans. 2*, 296 (1972); (e) M. Cinquini and S. Colonna, *Synthesis*, 259 (1972); (f) S. Iriuchijima and G. Tsuchihashi, *ibid.*, 588 (1970); (g) G. Tsuchihashi and S. Iriuchijima, *Bull. Chem. Soc. Jap.*, **43**, 2271 (1970); (h) K. C. Tin and T. Durst, *Tetrahedron Lett.*, 4643 (1970); (i) S. Iriuchijima and G. Tsuchihashi, *ibid.*, 5259 (1969); (j) R. N. Loeppky and D. C. K. Chang, *ibid.*, 5415 (1968); (k) M. Cinquini, S. Colonna, and F. Montanari, *Chem. Commun.*, 607 (1969); (l) M. Hojo and Z. Yoshida, *J. Amer. Chem. Soc.*, **90**, 4496 (1968); (m) D. L. Tuleen and R. M. White, *J. Tenn. Acad. Sci.*, **42**, 111 (1967).

(3) (a) M. Cinquini, S. Colonna, R. Fornasier, and F. Montanari, *J. Chem. Soc., Perkin Trans. 1*, 1886 (1972); (b) S. Iriuchijima, M. Ishibashi, and G. Tsuchihashi, *Bull. Chem. Soc. Jap.*, **46**, 921 (1973).

(4) B. B. Jarvis and J. C. Saukaitis, *J. Amer. Chem. Soc.*, **95**, 7708 (1973). (Paper II in the series on Nucleophilic Displacement Reactions on Halogen Atoms.)

(5) (a) D. L. Tuleen and T. B. Stephens, *J. Org. Chem.*, **34**, 31 (1969); (b) G. E. Wilson, Jr., and M. G. Huang, *ibid.*, **35**, 3002 (1970).

(6) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," 2nd ed, Cornell University Press, Ithaca, N. Y., 1969, p 443.

(7) J. Hine, "Physical Organic Chemistry," 2nd ed, McGraw-Hill, New York, N. Y., 1962, p 173.

(8) E. Kuhle, *Synthesis*, 561 (1970).

(9) L. A. Carpino, L. V. McAdams, III, R. H. Rynbrant, and J. W. Spiewak, *J. Amer. Chem. Soc.*, **93**, 476 (1971).

(10) C. Y. Meyers and G. J. McCollum, *Tetrahedron Lett.*, 289 (1973).

(11) In refluxing methanol, **2a** reacts slowly with triphenylphosphine to give a 1:1 ratio of **3a**:**3b**; under the same conditions, $(Me_2N)_3P$ reacts very rapidly with **1a** to give the same 1:1 ratio of **3a**:**3b**. Similar results were observed in the reduction of benzotrichloride to benzal chloride with these phosphines.[12]

(12) I. M. Downie and J. B. Lee, *Tetrahedron Lett.*, 4951 (1968).

(13) B. B. Jarvis, S. D. Dutkey, and H. L. Ammon, *J. Amer. Chem. Soc.*, **94**, 2136 (1972).

(14) S. Wolfe, *Accounts Chem. Res.*, 5, 102 (1972).

(15) Recent examples for use in organic synthesis are (a) I. Kuwajima and Y. Fukuda, *Tetrahedron Lett.*, 327 (1973); (b) G. Tsuchibashi, S. Mitamura, S. Inoue, and K. Ogura, *ibid.*, 323 (1973); (c) G. Tsuchihashi and K. Ogura, *Bull. Chem. Soc. Jap.*, **45**, 2023 (1972); (d) C. A. Kingsbury, *J. Org. Chem.*, **37**, 102 (1972); (e) T. Durst, R. Viau, R. V. D. Elzen, and C. H. Nguyen, *Chem. Commun.*, 1334 (1971). For leading references to the stereochemistry of base-catalyzed H–D exchange reactions in sulfoxides, see (f) M. B. D'Arnone and J. E. Brauman, *J. Chem. Soc., Chem. Commun.*, 399

(1973); (g) R. Viau and T. Durst, *J. Amer. Chem. Soc.*, **95**, 1346 (1973); (h) K. Nishihata and M. Nishio, *Tetrahedron Lett.*, 4839 (1972).
(16) (a) B. J. Hutchinson, K. K. Anderson, and A. R. Katritsky, *J. Amer. Chem. Soc.*, **91**, 3839 (1969); (b) R. R. Fraser, F. J. Schuber, and Y. Y. Wigfield, *ibid.*, **94**, 8785 (1972).
(17) The ratios presented in Table I are quite reproducible and were shown not to vary in the presence or absence of triethylamine. The product sulfoxides **3a** and **3b** also were shown not to undergo appreciable epimerization under the reaction conditions.
(18) J. R. Hanson and E. Premuzic, *Angew. Chem., Int. Ed. Engl.*, **7**, 247 (1968).
(19) R. E. Erickson and R. K. Holmquist, *Tetrahedron Lett.*, 4209 (1969).
(20) J. K. Kochi and D. D. Davis, *J. Amer. Chem. Soc.*, **86**, 5264 (1964).
(21) J. K. Kochi and P. E. Mocaldo, *J. Org. Chem.*, **30**, 1134 (1965).
(22) D. G. Holah and J. P. Fackler, Jr., *Inorg. Syn.*, **20**, 26 (1967).
(23) The α,α-dichloro sulfoxides have S–O stretching frequencies near 1100 cm^{-1}, which is *ca.* 50 cm^{-1} higher than normal: K. Nakanishi, "Infrared Absorption Spectroscopy," Holden-Day, San Francisco; California, 1962, p 54.
(24) Our results here closely parallel those reported elsewhere.[10]
(25) W. R. Waldron and E. E. Reid, *J. Amer. Chem. Soc.*, **45**, 2399 (1923).
(26) I. Heilbron, "Dictionary of Organic Compounds," Vol. 4, Oxford University Press, New York, N. Y., 1965, p 2436.
(27) M. D. Wolfinger, Ph.D. Thesis, Northwestern University, 1968.

Desulfurization of β-Keto Sulfides and Thiocyanates with Tris(dialkylamino)phosphines[1a]

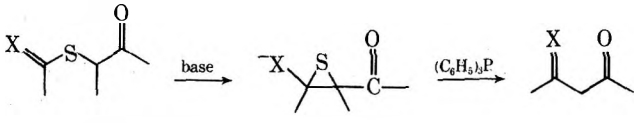
David N. Harpp* and S. Martin Vines[1b]

Department of Chemistry, McGill University, Montreal, Canada

Received August 10, 1973

Tris(dimethylamino)phosphine (**4a**) desulfurizes β-keto sulfides to afford a variety of products including ketones and enol ethers. The mechanism probably involves a phosphonium salt. Benzyl thiocyanate was readily desulfurized by **4a** in a complex reaction to afford benzyl cyanide and dibenzyl sulfide as the main products.

The reaction of trivalent phosphorus compounds with a wide variety of sulfur-containing molecules has received considerable attention in recent years, particularly as a technique for modifying the substrate by extrusion of the divalent sulfur atom.[2] While simple sulfides are inert to phosphines and phosphites, activated sulfides of type **1** are desulfurized in the presence of triphenylphosphine and base.[3] The reaction is widely applicable to the preparation of secondary vinylogous amides or enolizable β-diketones **3**. It has been suggested that **1** is first converted to an episulfide **2** which is then desulfurized.[4]

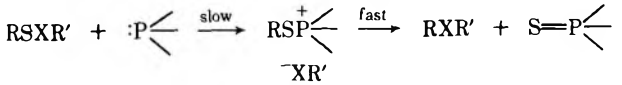


1, X = O, N– 2 3

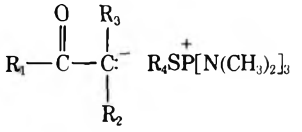
Related work has shown that tris(dialkylamino)phosphines (**4**) are particularly useful reagents for smoothly extruding sulfur from a variety of molecules. These include disulfides,[2] thiosulfonates ($RSSO_2R$),[5] sulfenyl thiosulfonates ($RSSSO_2R$),[5b] thiosulfinate esters [RS(=O)SR],[6] trisulfides,[7] sulfenimides [$RSN(C(=O)R)_2$],[8] and sulfenate esters (RSOR).[9]

$(R_2N)_3P$
4a, R = CH_3
b, R = CH_2CH_3

The desulfurization reactions are in some cases known to be two-step processes[2] as shown below.



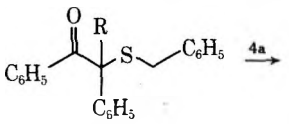
Reactions of β-Keto Sulfides. If the above pathway could be used to generate carbanions which fulfilled the dual role of leaving group and nucleophile, a new procedure for carbon–carbon bond formation would be available. Accordingly, a number of β-keto sulfides were prepared and their reaction with tris(dimethylamino)phosphine (**4a**) was examined. Previous work[2,5-9] suggested that the proposed reaction would probably involve a phosphonium salt intermediate **5**.[15a-c]



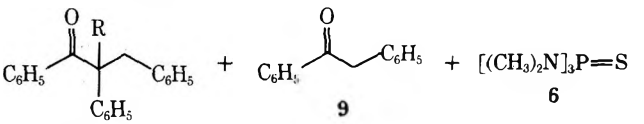
5

To facilitate displacement of the carbanion of **5**, a phenyl group was used at R_2. It appeared that a benzyl moiety at R_4 might encourage easy displacement of tris(dimethylamino)phosphine sulfide (**6**). α-Benzoyl-α-phenylmethyl benzyl sulfide (**7a**)[10] reacts extremely slowly with phosphine **4a** (in a variety of solvents), giving deoxybenzoin ($C_6H_5COCH_2C_6H_5$, **9**) as the principal product.

When the reaction was carried out in the absence of solvent, the starting materials were consumed in less than 1 hr to give three products as analyzed by quantitative vpc: 1-benzoyl-1,2-diphenylethane (**8a**, 69%), deoxybenzoin (**9**, 22%), and tris(dimethylamino)phosphine sulfide (**6**, 86%). **8a** was subsequently isolated in 43% yield.



7a, R = H
b, R = D



8a, R = H **9** **6**
b, R = D

It appears that **5** ($R_1 = R_2 = C_6H_5$; $R_4 = C_6H_5CH_2$; R_3 = H) is formed, but that the anion is partially diverted by proton abstraction to give deoxybenzoin (**9**). The proton attached to the α carbon atom in **7a** is likely to be the one abstracted. This was confirmed by isolation of $PhCOCD_2Ph$ after the reaction of keto sulfide **7b** with aminophosphine.

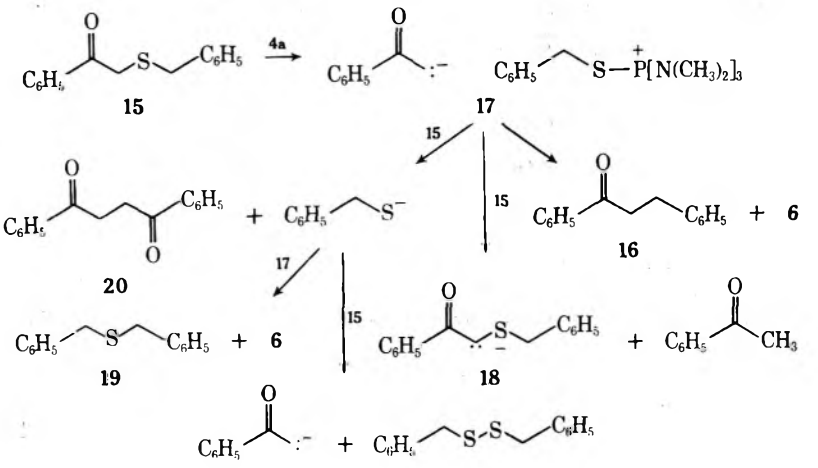
To determine whether alkylative coupling could occur for a β-keto sulfide that did not have a benzyl group as the second substituent on the sulfur atom, α-benzoyl-α-

Table I
Reaction of Tris(dimethylamino)phosphine with β-Keto Sulfides

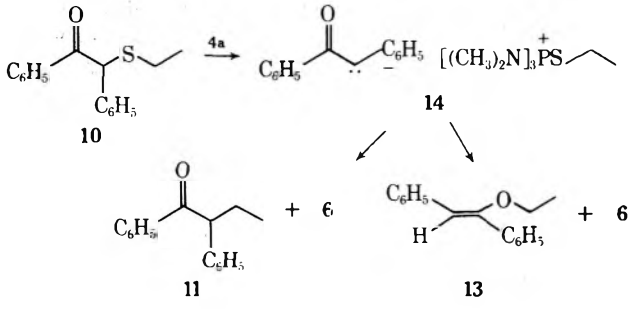
	Starting material			Products (%)			
	$R_1CCHR_2SCH_2R_3$			$R_1CCHR_2CH_2R_3$	$C_6H_5CCH_2R_2$	$[(CH_3)_2N]_3P{=}S$	
Compd	R_1	R_2	R_3			(6)	Other
7a	C_6H_5	C_6H_5	C_6H_5	69[a] (43)[b]	22[a] (12)[b]	86[a]	
10	C_6H_5	C_6H_5	CH_3	31[a]	9[a]	67[a]	**13**, 14[a]
							12, 28[c]
15	C_6H_5	H	C_6H_5	5[a]	30[a]	47[a]	$(C_6H_5CH_2)_2S$, 50[a]

[a] Crude yield (estimated by isolation of product and/or quantitative vpc and nmr of impure fractions). [b] Isolated pure. [c] Per cent of vpc integral trace.

Scheme I



phenylmethyl ethyl sulfide (**10**) was prepared[10] and treated with aminophosphine **4a**. Although 1-benzoyl-1-phenylpropane (**11**) was formed in reasonable yield (Table I), it proved difficult to isolate, as it and deoxybenzoin (**9**) behave in a very similar manner on column, thin layer, and gas chromatography. A third unidentified material **12** also had very similar chromatographic properties. The fourth product, *trans*-1-ethoxy-1,2-diphenylethene (**13**), gives further credence to the carbanion mechanism.[11]



In an attempt to simplify the mixture of products formed in the desulfurization of **10**, effects of solvent on the reaction were considered. It has been reported[12] that C-alkylation of ketonic anions is promoted by the use of hydroxylic solvents (such as water, polyfluorinated alcohols, or phenols). It is unlikely that the proportion of ketone **11** could be increased by the use of such solvents, as the anion of **14** would become irreversibly protonated, giving deoxybenzoin as the major product. Polar aprotic solvents, such as *N,N*-dimethylformamide or dimethyl sulfoxide, have a tendency to increase the proportion of O-alkylation.[12] Finally, use of volatile aprotic solvents such as benzene or 1,4-dioxane gives slow desulfurization to form a product mixture very similar to that obtained by treatment of β-keto sulfide **10** with neat aminophosphine.

It was found that temperature has little effect on product distribution; the major effect is on reaction rate. This observation suggests that the rate-determining step is the attack of phosphorus on sulfur to give **14**, or (less likely) that this step is fast and that the subsequent reactions of this intermediate all have similar thermodynamic parameters.

To test whether the α-phenyl group is required for desulfurization to occur, α-benzoylmethyl benzyl sulfide (**15**) was prepared[13] and treated with aminophosphine **4a** (Scheme I) to give benzyl sulfide (50%) as the only product isolable from the reaction. The reaction was slower than for the previous keto sulfides; starting material (2%) was present even after heating for 3 hr at 150°. Acetophenone (30%) was the other major product; only a small amount of 1-benzoyl-2-phenylethane (**16**, 5%) was produced.

The observed products (**6**, **16**, and **19**) can be rationalized (Scheme I) in a similar fashion as in the reaction of **7** and **10** with phosphine **4a**. This would yield **17**, the anion of which would not in this case be expected to attack starting material displacing benzyl mercaptide ion, since the more stable deoxybenzoin anion formed from **7a** and **10** does not undergo such an intermolecular reaction. Ketone **20** in fact is not observed in the reaction mixture.[14]

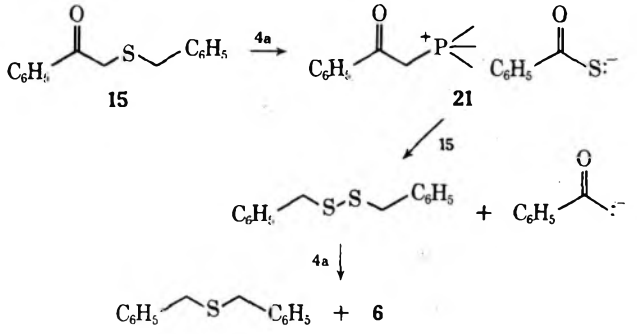
A plausible source of benzyl mercaptide ion involves an S_N2 process (Scheme II) analogous to that proposed for some reactions of trialkyl phosphites with aromatic thiocyanates.[15c,d] If this type of mechanism were in operation, mercaptide ion formation should be encouraged by the use of a β-keto sulfide containing an α-phenyl moiety. Also, if an ion pair such as **17** were formed, its fate should be similar to that of the corresponding ion pairs invoked as intermediates in the desulfurization of the α-phenyl-β-keto sulfides **7** and **10**. Finally, if phosphorus were attacking carbon, a low yield of phosphine sulfide **6** would be expected; this was, in fact, observed.

Table II
Reaction of Aminophosphines with RSXR

X	pK_a of RXH	X	pK_a of RXH
$-SO_2-$[a,b]	2[5]	$-S-$[a]	10[2]
$-\overset{O}{\overset{\|}{S}}-$[a,b]	>2[6]	$-O-$[a]	17[9]
		$-CH_2\overset{O}{\overset{\|}{C}}-$[b,c]	19
$-SS-$[a]	8[7]	$-CH_2CO_2-$[d]	23
$-NHCO-$[a]	9[8]		

[a] Smooth desulfurization to give RXR in good yield. [b] If X can provide an ambident anion (*e.g.*, $-SO_2^-$), more than one product may be formed. [c] Some desulfurization, competition from side reactions. [d] No reaction.

Scheme II



A direct substitution reaction such as that invoked in the thiocyanate–phosphine reaction would be encouraged by the reduction in crowding at the α carbon atom produced by removal of the phenyl group. Removal of this group would also increase the activation energy for the attack of phosphorus on sulfur to displace the carbanion of **17**, which is less stable than the anion formed from **7a** and **10**. This is probably the major factor in changing the direction of the reaction. No other compounds could be isolated from the reaction mixture because several of the products had similar chromatographic properties.

The reaction of S-substituted thioglycollic acid esters with aminophosphines was also investigated. Ethyl 4-phenyl-3-thiabutanoate (**22**)[16] gave no reaction with neat tris(dimethylamino)phosphine (**4a**), even when a mixture of the two compounds was maintained at high temperature for extended periods of time. The lack of reactivity of the ester can be rationalized by the relatively high pK_a associated with $^-:CH_2CO_2Et$ (pK_a = 24),[17] which must be displaced by phosphine for desulfurization to occur. The anion of **17** is more stable (pK_a = 19),[17] and is hence a better leaving group than the anion that must form from **22**. A nucleophilic substitution reaction involving attack of phosphine on the carbon atom α to the carbonyl group would be much slower for the ester than for the ketone.[18] Thus, the limit of the reaction of aminophosphines with sulfur-containing molecules emerges (Table II). Aminophosphines will not displace groups with a pK_a ≥ 20. Where the pK_a is near 20, higher temperatures and neat reactants are usually required to effect displacement.

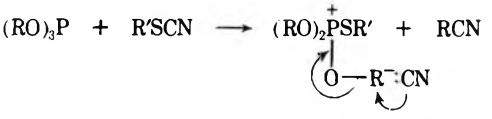
Reaction of Thiocyanates. Cyanide ion is similar to sulfide ion in that it is a good leaving group and nucleophile. It was thus felt that thiocyanates might be converted readily to nitriles on treatment with an aminophosphine. Early reports exist in the literature for the desulfurization of thiocyanates[20] and isothiocyanates[21] on treatment with trialkylphosphines, although few experimental data were given. More recently, the reactions of thiocyanates with trialkyl phosphites have been studied.[15]

Table III
Reaction of Benzyl Thiocyanate with Aminophosphine 4a

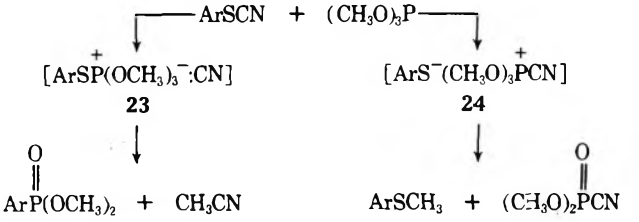
Solvent	Time,[a] min	Products, %[b] $(C_6H_5CH_2)_2S$	$C_6H_5CH_2CN$	$[(CH_3)_2N]_3P{=}S$
None	40	45	9	32
Acetonitrile	40	42	17	30
Dichloromethane	30	25	22	38
p-Dioxane	60	25	11	41
Benzene[c]	130	21	6	28

[a] Time for the reaction mixture to attain constant composition (vpc). [b] Determined by quantitative vpc. [c] Reflux.

Desulfurization accompanied by rearrangement was observed.[15b] Sheppard obtained evidence that the rearrangement occurs through an ionic pathway and proposed the following mechanism.[15b]



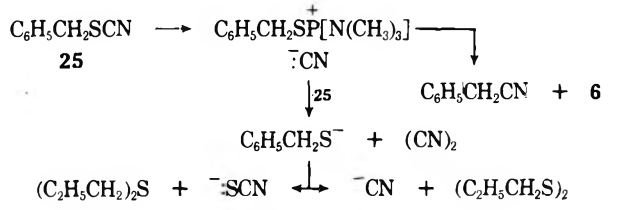
Pilgram and Phillips, in a detailed study of the reaction of a number of aryl thiocyanates with trimethyl phosphite, found that another reaction path is possible.[15c] Instead of preferentially attacking sulfur to form intermediate **23**, phosphorus can attack the carbon atom of the thiocyanate group, displacing a mercaptide ion to give intermediate **24**.



Treatment of benzyl thiocyanate (**25**) with tris(dimethylamino)phosphine gave an immediate exothermic reaction that produced a deep red color, even at room temperature. Vapor phase chromatography indicated that the reaction mixture was extremely complex (at least ten products). Preparative thin layer chromatography yielded only benzyl sulfide (**26**) and tris(dimethylamino)phosphine sulfide (**6**) as isolable materials. A large quantity of brown oil was obtained which contained many components. Vapor phase chromatography showed that benzyl cyanide was one of the major products.

The reaction was repeated in a variety of solvents. The yields of the major constituents of the mixture are shown below (Table III). The rate of formation of the red color increased with the polarity of the solvent.

If the appearance of the red color is indicative of the rates of the major reaction pathways, then it would seem that the mechanism is ionic. A plausible pathway is outlined below.



Benzyl cyanide could be formed by attack of aminophosphine on the sulfur atom, followed by attack of the displaced cyanide ion on the intermediate phosphonium

ion, in accord with the mechanisms of the other desulfurization reactions discussed. Attack of cyanide on this phosphonium ion may also give some isocyanide; although vpc did not rule out the presence of this compound, none was isolated.

If cyanide attacks a second molecule of thiocyanate instead of the phosphonium ion, it could displace mercaptide ion. The mercaptide ion could then attack the starting material to give either the observed sulfide or benzyl disulfide. Again, vpc did not rule out the presence of disulfide, but it was not isolated from the reaction mixture; if formed, it would be desulfurized by aminophosphine to give benzyl sulfide.[2]

Attack by **4a** on the carbon atom of the thiocyano group is also possible.[15c] Such an attack would lead to displacement of mercaptide ion, which could react with **25** to give benzyl sulfide.

Experimental Section[22]

Action of Tris(dimethylamino)phosphine on β-Keto Sulfides. α-Benzoyl-α-phenylmethyl Benzyl Sulfide. A. In the Presence of a Solvent. Refluxing a solution of α-benzoyl-α-phenylmethyl benzyl sulfide (**7a**, 0.318 g, 1.0 mmol) and tris(dimethylamino)-phosphine (**4a**, 0.16 g, 1.0 mmol) in benzene or 1,4-dioxane (1 ml) for 8 hr gave small amounts of deoxybenzoin (**9**) as the major product (qualitative vpc). A similar result was obtained using dichloromethane as solvent, either stirring for 24 hr at room temperature or refluxing for 12 hr.

B. Without Solvent. α-Benzoyl-α-phenylmethyl benzyl sulfide (**7a**, 1.00 g, 3.2 mmol) and tris(dimethylamino)phosphine (**4a**, 0.510 g, 3.2 mmol) were heated on an oil bath at 120°. After 30 min all starting material had been consumed (vpc). The mixture was then chromatographed on silica gel (60–100 mesh) using hexane (100 ml), hexane–dichloromethane mixtures (9:1, 100 ml; 4:1, 100 ml; 3:2, 500 ml; 1:1, 500 ml) and dichloromethane (100 ml) as eluents. The fractions collected were monitored by vpc. Separations were not completely efficient; combination of the first eluents and crystallization from ethanol gave 1-benzoyl-1,2-diphenylethane (**8a**, 0.39 g, 43%) as colorless needles, mp and mmp 119–120° (lit.[23] mp 120–121°). It was identical in all respects (vpc, tlc, ir, nmr) with an authentic sample. A later fraction was crystallized from aqueous ethanol to afford deoxybenzoin (**9**, 0.075 g, 12%), mp and mmp 55–56°, identical in all respects with an authentic sample.

α-Benzoyl-α-deuteriomethyl Benzyl Sulfide (7b). β-Keto sulfide **7a** (2.0 g) was crystallized from deuterioethanol (EtOD) to which a small piece of sodium had been added. The product was dissolved in carbon tetrachloride (10 ml); the resultant solution was filtered and evaporated to give, after crystallization (EtOH), the title compound **7b** (1.4 g, 70%) as colorless needles, mp 73–74°, and no detectable absorption in the nmr spectrum at δ 4.72, suggesting quantitative deuteration at the α position.

A portion of this material (0.79 g, 2.5 mmol) was mixed with tris(dimethylamino)phosphine (**4a**, 0.456 g, 2.8 mmol) and heated on an oil bath at 150° for 1 hr. The resulting mixture was chromatographed to give (a) 1-benzoyl-1-deuterio-1,2-diphenylethane (**8b**, 0.389 g, 55%), mp 121–123° after crystallization (ethanol) (mmp with nondeuterated material 121–122°, identical with **8a** by tlc and vpc); (b) $C_6H_5COCD_2C_6H_5$ (**9**, 0.045 g, 9%), mp 47–51°, pure by tlc (CCl_4) and vpc, containing 80% deuterium at the benzylic position (nmr, CCl_4); (c) a mixture of these two materials (0.130 g, tlc, vpc); and (d) tris(dimethylamino)phosphine sulfide (**6**, 0.340 g, 81%), identified by vpc and nmr.

α-Benzoyl-α-phenylmethyl Ethyl Sulfide. α-Benzoyl-α-phenylmethyl ethyl sulfide (**10**, 0.128 g, 0.5 mmol) and tris(dimethylamino)phosphine (**4a**) were mixed and heated on an oil bath for various time intervals and temperature conditions. Above 120° using varying molar amounts of phosphine (consumed in ~10 min) virtually constant yields of **9**, **11**, **12**, and **13** were obtained.

The reaction was also examined using benzene, 1,4-dioxane, and *N,N*-dimethylformamide as solvents (1 ml) and 1 mmol of each of the starting materials. Again, yields were approximately constant with each solvent.

Isolation of Products. α-Benzoyl-α-phenylmethyl ethyl sulfide (**10**, 640 mg, 2.5 mmol) and tris(dimethylamino)phosphine (**4a**, 450 mg, 2.7 mmol) were heated on an oil bath at 150° for 1 hr. The resulting mixture was chromatographed on silica gel (60–100 mesh, 60 g) using hexane (500 ml) and hexane–dichloromethane mixtures (9:1, 2 l.; 8:2, 2 l.; 7:3, 1 l.; 6:4, 1 l.; and 5:5, 1 l.) as eluents. The fractions collected were monitored by vpc. Separations were not completely efficient; however, the first fraction, a colorless oil (80 mg), was pure by tlc (hexane) and vpc; ν_{max} (liquid film) 2978, 1638, 1604, 1689, 1497, 1452, 1120 (v broad), 925, 772, and 700 cm^{-1}; nmr gave signals (CCl_4) at δ 1.8–2.8 (multiplet, 10 H), 3.8 (singlet, 1 H), 6.1 (quartet, 2 H), and 8.7 (triplet, 3 H); mass spectrum showed P^+ at 224. This information indicates that the material is an enol ether, $C_6H_5CH{=}C(C_6H_5)OC_2H_5$. Identification of a band characteristic of trans alkyl enol ethers in the ir[25] at 925 cm^{-1} suggests that this compound is *trans*-**1-ethoxy-1,2-diphenylethylene** (**13**, 14%). The second fraction was rechromatographed to give a sample of 1-benzoyl-1-phenylpropane (**11**, 61 mg, 11%) (vpc, tlc, nmr); after crystallization (EtOH) mp and mmp 49–52° (lit. mp 57°,[23c] 58°[24]); a mixture of **11** and **12** (160 mg) (vpc, tlc) was also obtained. Ketone **11** was also present in the next two fractions (vpc, tlc, nmr). Tris(dimethylamino)phosphine sulfide (**6**, 327 mg, 67%) was isolated in a further fraction (pure by vpc and tlc).

α-Benzoylmethyl Benzyl Sulfide. α-Benzoylmethyl benzyl sulfide (**15**, 2.42 g, 10 mmol) and tris(dimethylamino)phosphine (**4a**, 1.80 g, 11 mmol) were heated on an oil bath at 150° for 3 hr. The resulting mixture was chromatographed on silica gel (60–100 mesh) (250 g) using as solvents hexane (1.5 l.), hexane–dichloromethane mixtures (1:10, 1 l.; 1:9, 1 l.; 3:17, 1 l.; 1:4, 1 l.; 3:7, 1 l.; 2:3, 1 l.; 1:1, 1 l.; 7:3, 1 l.), dichloromethane (1 l.), chloroform (1 l.), ethyl acetate (1 l.), and methanol (1 l.). Efficient separation proved impossible; however, dibenzyl sulfide (540 mg, 50%) was isolated as yellow prisms, mp and mmp 47–49°, identical in all respects (tlc in benzene, vpc, ir, nmr) with an authentic sample of the sulfide.

Further fractions were obtained containing acetophenone, dibenzyl sulfide, 1-benzoyl-2-phenylethane (**16**),[26] starting material, and traces of other unidentified materials (vpc, tlc in cyclohexane or benzene, nmr).

Tris(dimethylamino)phosphine sulfide (**6**, 911 mg, 47%) was isolated in an almost pure state. Large quantities of polar material containing many unidentified components were also obtained.

Benzyl Thiocyanate. Benzyl thiocyanate (0.149 g, 1 mmol) and tris(dimethylamino)phosphine (0.163 g, 1 mmol) were mixed. An immediate reaction ensued, turning the mixture deep red. Mixing these materials in methylene chloride (1 ml) or acetonitrile (1 ml) gave a similar result. When benzene (1 ml) was used as solvent the reaction was much slower; the mixture turned yellow, orange, then red.

The methylene chloride solution obtained in this manner was separated into five fractions by preparative tlc on silica gel [solvents cyclohexane–ethyl acetate (1:1) and then benzene].

Dibenzyl sulfide, identical with an authentic sample (vpc, tlc, nmr, ir), and tris(dimethylamino)phosphine sulfide (**6**) (vpc, nmr) were isolated.

The other three fractions contained many components that were not identified, as they proved inseparable.

The reaction was then repeated in a variety of solvents; the product mixtures were analyzed for benzyl sulfide, benzyl cyanide, and **6** by quantitative vpc, using cumene as an internal standard. The results of these experiments are summarized in Table III.

Acknowledgment. We wish to thank the National Research Council of Canada for financial support of this work.

Registry No.—**4a**, 1608-26-0; **7a**, 23343-23-9; **7b**, 50311-41-6; **8b**, 50311-42-7; **10**, 16222-12-1; **15**, 2408-88-0; benzyl thiocyanate, 3012-37-1.

References and Notes

(1) (a) Organic Sulfur Chemistry. XVIII. For part XVII, see D. N. Harpp and T. G. Back, *J. Org. Chem.*, **38**, 4328 (1973). (b) Holder of NRCC Bursary, 1971–1972.
(2) D. N. Harpp and J. G. Gleason, *J. Amer. Chem. Soc.*, **93**, 2437 (1971), and references cited therein.
(3) M. Roth, P. Dubs, E. Gotschi, and A. Eschenmoser, *Helv. Chim. Acta*, **54**, 710 (1971).
(4) (a) C. C. J. Culvenor, W. C. Davies, and N. S. Heath, *J. Chem. Soc.*, 282 (1949); (b) R. E. Davis, *J. Org. Chem.*, **23**, 1767 (1958); (c) R. D. Schuetz and R. L. Jacobs, *ibid.*, **23**, 1799 (1958); (d) N. P. Neureiter and F. G. Bordwell, *J. Amer. Chem. Soc.*, **81**, 578 (1959); (e) D. B. Denny and M. J. Boskin, *ibid.*, **82**, 4736 (1960).
(5) (a) D. N. Harpp and J. G. Gleason, *Tetrahedron Lett.*, 1447 (1969); (b) D. N. Harpp, J. G. Gleason, and D. K. Ash, *J. Org. Chem.*, **36**, 322 (1971).

(6) J. E. McCormick and R. S. McElhinney, *J. Chem. Soc., Perkin Trans. 1*, 2795 (1972); D. N. Harpp and J. G. Gleason, unpublished results.
(7) D. N. Harpp and D. K. Ash, *Chem. Commun.*, 811 (1970).
(8) D. N. Harpp and B. A. Orwig, *Tetrahedron Lett.*, 2691 (1970).
(9) D. H. R. Barton, G. Page, and D. A. Widdowson, *Chem. Commun.*, 1466 (1970); D. N. Harpp and B. A. Orwig, unpublished results.
(10) D. N. Harpp and P. Mathiaparanam, *J. Org. Chem.*, **37**, 1367 (1972).
(11) Investigation of the alkylation of the anion of ethyl acetoacetate with alkyl halides suggests that increased SN2 activity of the alkylating agent is correlated with decreased O/C activity toward nucleophilic substitution.[12] This is in agreement with our observation that when two keto sulfides (which give the same ketonic anion) undergo desulfurization, ethyl keto sulfide **10** gives significant quantities of enol ether while the benzylic homolog **7a** does not.

$C_6H_5CCH(C_6H_5)SR$
7a, R = $C_6H_5CH_2$
10a, R = CH_3CH_2

(12) W. J. LeNobie and J. E. Piorta, *Tetrahedron Lett.*, 1087 (1966); W. J. LeNoble and H. F. Morris, *J. Org. Chem.*, **34**, 1969 (1969).
(13) L. M. Long, *J. Amer. Chem. Soc.*, **68**, 2159 (1946).
(14) It should be noted that while ketone **20** was not observed as a product in the reaction, thereby precluding significant benzyl mercaptide formation by this route, benzyl mercaptide does react with starting material **15** to give benzyl disulfide. This disulfide is known to desulfurize with **4a** to give benzyl sulfide.[2]
(15) (a) J. Michalski and J. Wieczorkowski, *Bull. Acad. Pol. Sci., Cl.* **3**, 4279 (1956); *Chem. Abstr.*, **51**, 4266 (1957). (b) W. A. Sheppard, *J. Org. Chem.*, **26**, 1460 (1961). (c) K. Pilgram and D. A. Phillips, *ibid.*, **30**, 2388 (1965). (d) This pathway contrasts with our initial mechanism (*vide supra*) as well as that of Borowitz[15e] on an analogous substrate. (e) I. J. Borowitz and R. Virkhaus, *J. Amer. Chem. Soc.*, **85**, 2183 (1963).
(16) (a) K. Schlogl, F. Wessely, and H. Woidich, *Monatsh. Chem.*, **87**, 425 (1956); (b) A. Ghavveau and R. Mathis-Noel, *Ann. Fac. Sci. Univ. Toulouse Sci. Math. Sci. Phys.*, **25**, 147 (1961); *Chem. Abstr.*, **60**, 11885*h* (1961); (c) C. Berse and G. Dupuis, *Can. J. Chem.*, **47**, 2174 (1965).
(17) (a) J. B. Conant and G. W. Wheland, *J. Amer. Chem. Soc.*, **54**, 1212 (1932); (b) W. K. McEwan, *ibid.*, **58**, 1124 (1936); (c) R. G. Pearson and R. L. Dillon, *ibid.*, **75**, 2439 (1953); (d) A. Streitweiser Jr., W. C. Langworthy, and J. I. Bravman, *ibid.*, **85**, 1761 (1963).
(18) For the analogous reactions of α-chloroacetophenone and ethyl chloroacetate with potassium iodide in acetone, exchange is about eight time more rapid for the former.[19]
(19) J. B. Conant, W. R. Kirner, and R. F. Hussey, *J. Amer. Chem. Soc.*, **47**, 488 (1925).
(20) A. W. Hofmann, *Ann. Chem. Pharm., Suppl. I*, 53 (1861).
(21) A. W. Hofmann, *Ber.*, **3**, 766 (1870).
(22) Gas chromatographic analyses (vpc) were performed on an F & M Model 5750 research chromatograph equipped with a Perkin-Elmer Model 194B printing integrator. Two 6 ft × 0.125 in. stainless steel column were used: 10% silicon gum rubber UC-W98 on Diaport S (80–100 mesh) and SE-30 ultraphase (10% by weight) on Chromosorb W AW/DMCS 80–100 mesh. Thin layer chromatographic analyses were performed on Eastman chromatogram sheets 6060 [silica gel with fluorescent indicator on poly(ethylene terephthalate) support; polyvinyl alcohol binder]. Solvent systems used are indicated in the text. Common intermediates were obtained from commercial sources and were purified as necessary. Melting points were obtained on a Gallenkamp apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 257 grating infrared spectrophotometer. Spectra were calibrated with 3027- and 1601-cm^{-1} bands of a polystyrene film reference. Refractive indices were measured on a Carl Zeiss 38341 refractometer at room temperature. Nuclear magnetic resonance (nmr) spectra were recorded on a Varian Associates T-60 spectrophotometer. All data are given in parts per million relative to TMS (used as an internal standard). Mass spectra were recorded on an AE1-MS-902 mass spectrometer equipped with a direct insertion probe.
(23) (a) S. Miyano and Y. Sako, *Chem. Pharm. Bull.*, **13**, 1372 (1965); (b) F. Klingemann, *Justus Liebigs Ann. Chem.*, **275**, 50 (1893); (c) H. Fiesselmann and J. Ribka, *Chem. Ber.*, **89**, 27 (1956); (d) E. J. Cragoe, Jr., A. M. Pietruszkiewicz, and C. M. Rbb, *J. Org. Chem.*, **23**, 1971 (1958).
(24) V. Meyer and L. Oelkers, *Ber.*, **21**, 1297 (1888).
(25) S. I. Miller, *J. Amer. Chem. Soc.*, **78**, 6091 (1956).
(26) R. Adams, J. W. Kem, and R. L. Schringer, "Organic Syntheses," Collect. Vol. I; H. Gilman and A. H. Blatt, Ed., Wiley, New York, N. Y., 1964, p 101.

Sulfuric Acid Catalyzed Rearrangements of 1- and 3-Homoadamantanols

Jelena Janjatović, Danko Škare, and Zdenko Majerski*

Rudjer Bošković Institute, 41001 Zagreb, Yugoslavia

Received July 5, 1973

Both 1- and 3-homoadamantanol yield homoadamantane, 1- and 2-methyladamantane, and 1-adamantylcarbinol in the reactions with 75% sulfuric acid (70°). The mechanism very likely involves formation of the 1- and 3-homoadamantyl cations, followed by hydride transfers and rearrangements of the resulting classical homoadamantyl cations into the corresponding bridged cations. A simple, good-yield preparation of 1-homoadamantanol is described.

Reactions with sulfuric acid leading to adamantane derivatives attracted considerable attention in the last few years.[1-8] *endo*-2,6-Trimethylene-*exo*-2-norbornanol in sulfuric acid was reported to rearrange smoothly into 1-adamantanol,[1] bicyclo[3.3.1]nonane-2,7-diol into 2-oxaadamantane,[2] while 3-hydroxymethylbicyclo[3.3.1]nonan-7-ol produced a mixture of 2-adamantanol, di(2-adamantyl) ether, and adamantane.[3] 2-Hydroxy-2-methyladamantane in 98% sulfuric acid gave various mixtures of methyladamantanones or methyladamantanes and hydroxymethyladamantanes depending on the temperature.[4] Synthetically useful reactions are also encountered. Treatment of deltacyclane with sulfuric acid gave either 1- or 2-noradamantanol or noradamantane, depending on conditions.[5] The reaction of adamantane or 1-adamantanol with 96% sulfuric acid (80°) resulted in a 50% yield of adamantanone,[6a] providing a very convenient method for the functionalization of the methylene position of adamantane. Both adamantanone oxime[7] and lactone 4-oxahomoadamantan-5-one[8] with sulfuric acid were reported to give fair yields of 4-hydroxyadamantan-2-one.[9]

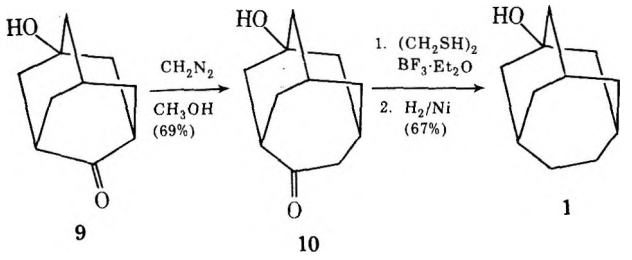
The reaction of adamantanols with sulfuric acid were extensively investigated by Geluk and Schlatmann.[6] 2-Adamantanol was shown to rearrange to 1-adamantanol (>98%) at 28° in concentrated sulfuric acid.[6a,10] An equilibrium mixture containing small amounts of 2-adamantanol was rapidly achieved from either direction. However, with 70% H_2SO_4 (90°) a mixture of 1,4-adamantanediol, adamantane, 1-hydroxy-4-adamantanone, and adamantanone was obtained.[6b] 1-Adamantanol, under essentially the same conditions, disproportionated into 1,3-adamantanediol and adamantane.[6b] The mechanism of these reactions appears to involve an intermolecular hydride transfer of a bridgehead hydrogen from one molecule of the starting alcohol to an adamantyl cation which is generated from another molecule of the alcohol and is transformed into adamantane.[11]

An analogous mechanism would be reasonably expected to operate in reactions of homoadamantyl alcohols with sulfuric acid. However, the 3- and 4-homoadamantyl cations, if formed, could rearrange into the corresponding nonclassical cations, which may lead to adamantane de-

rivatives. Such cations were reported to be involved as the intermediates in the acetolysis of chiral 1-adamantylcarbinyl-*1'-d* toxylate[12] and the $AlBr_3$-catalyzed rearrangement of homoadamantene.[13] Consequently, the product distribution in the sulfuric acid reaction of homoadamantyl alcohols should depend on the relative rates of the disproportionation reactions *vs.* the rearrangements of homoadamantyl cations.

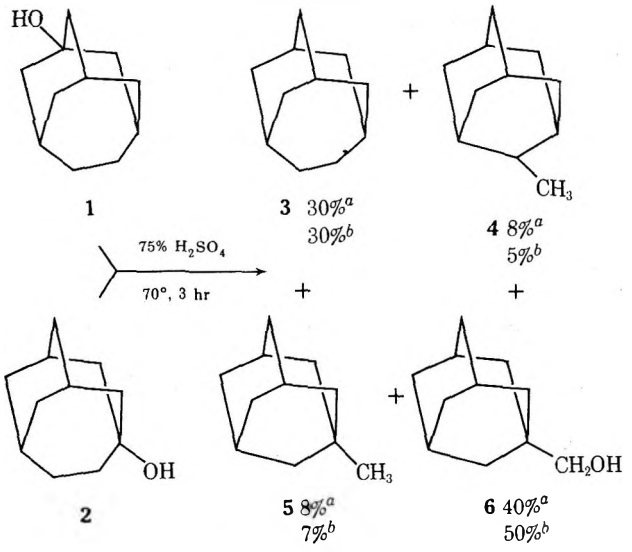
We wished to compare the reactions of bridgehead adamantanol and homoadamantanols with sulfuric acid under essentially the same conditions. 3-Homoadamantanol (**2**) can easily be prepared,[14] but a convenient synthesis[15] of 1-homoadamantanol (**1**) has not been reported according to our knowledge. As the starting material we chose readily available 1-hydroxy-4-adamantanone (**9**).[6c] Diazomethane homologation of **9** gave 1-hydroxy-4-homoadamantanone (**10**) in a 69% yield (Scheme I). However, the Clemmensen and the Wolff–Kishner reductions failed to give **1** in satisfactory yields. 1-Homoadamantanol (**1**) was obtained in a 67% overall yield from **10** by Raney nickel *desulfurization* of the corresponding *ethylene thioketal* (**11**).[16]

Scheme I



1-Homoadamantanol (**1**) or 3-homoadamantanol (**2**) was stirred vigorously in 75% sulfuric acid at 70° for 3 hr. In definite time intervals small samples were taken out from the reaction mixture and analyzed by glc. The final product distributions from **1** and **2** were quite similar (Scheme II).

Scheme II



[a] The main products of **1**.[17] [b] The main products of **2**.[17] An amount of polymer was also formed. The relative amounts of homoadamantane (**3**), 2-methyladamantane (**4**), and 1-methyladamantane (**5**) were found to increase with time at the expense of 1-adamantylcarbinol (**6**).

The methyladamantanes (**4** and **5**) were identified by glc using the internal standards; homoadamantane (**3**) and 1-adamantylcarbinol (**6**) were isolated by preparative glc and identified by comparison of their ^1H nmr, ir, and mass spectra with those of the authentic samples. Homoadamantane (**3**) and the methyladamantanes (**4** and **5**) were proved to be stable under the above conditions. 1-Adamantylcarbinol (**6**) was found to be the *only* alcohol present in both reaction mixtures on quenching the reaction after 10 min. Upon treatment of **6** with H_2SO_4 under the same conditions as used for **1** and **2** the following final product distribution was obtained: **3**, 23%; **4**, 3%; **5**, 8%; and unreacted **6**, 45%.[17]

Isomerization of **1** and **2** into **6** is not surprising. The homoadamantyl skeleton is known to be about 10 kcal/mol more strained than the adamantyl skeleton[18] and, therefore, **6** should be thermodynamically more stable than **1** and **2**. This is in accord with complete isomerization of 3-homoadamantyl acetate into 1-adamantylcarbinyl acetate in acetic acid containing *p*-toluenesulfonic acid.[14] However, under kinetically controlled conditions homoadamantyl products may be favored. Hydrolysis of 1-adamantylcarbinyl tosylate in aqueous diglyme in the presence of sodium carbonate produced virtually quantitatively 3-homoadamantanol.[14] The mechanism of the isomerization of **1** and **2** into **6** very likely involves the initial formation of the 1- and 3-homoadamantyl cations (Scheme III). This is probably followed by hydride transfers resulting in the isomerization of the 1 and 3 cations into each other and into the 2-, 4-, and 9-homoadamantyl cations. The 1,2-intramolecular hydride transfers are highly improbable to occur on the homoadamantyl skeleton.[19] As in the case of the adamantyl nucleus[20] the relationship between the vacant p orbital and the migrating hydride is very unfavorable.

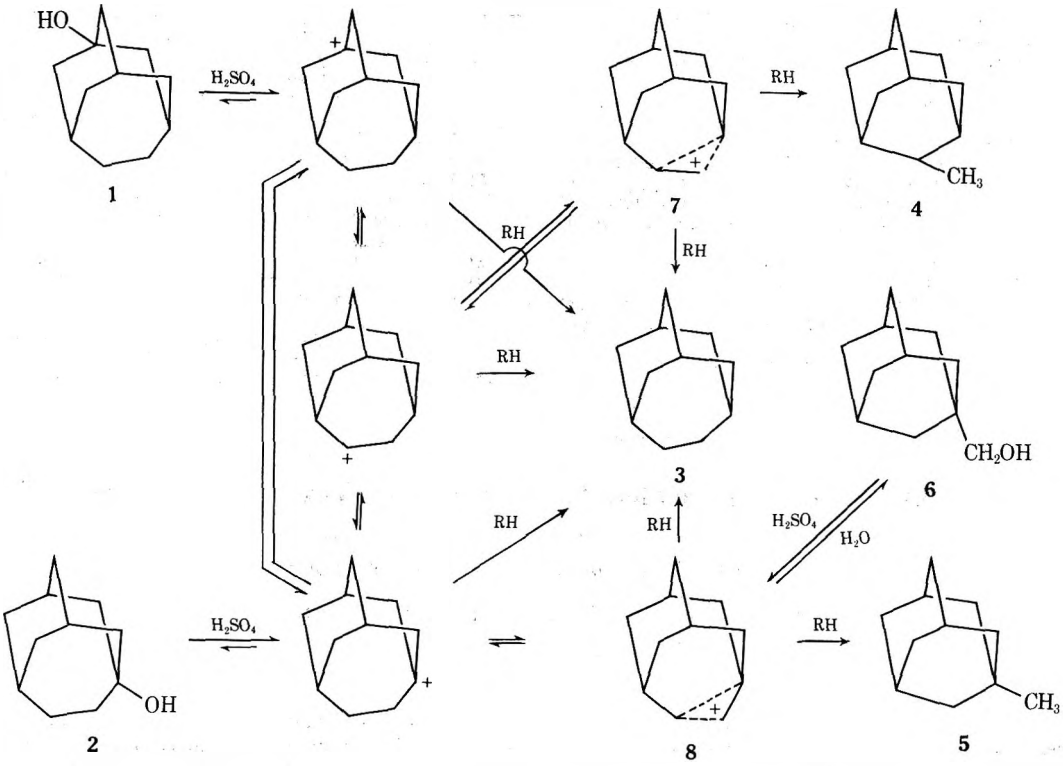
Total amounts of the hydrocarbons **3**–**5** are quite high regardless of the starting alcohol. Homoadamantane (**3**) can be formed from *any* homoadamantyl cation by a hydrogen abstraction from the products, polymer, or the starting alcohol. 1-Adamantylcarbinol (**6**), 1-methyladamantane (**5**), and 2-methyladamantane (**4**) could be formed either from the bridged homoadamantyl cations[12-14] **8** and **7** or from the primary 1- and 2-adamantylcarbinyl cations. Since simple primary carbonium ions appear to be energetically inaccessible under usual reaction conditions,[12,21] we suggest the nonclassical homoadamantyl cations **7** and **8** as the more plausible intermediates (Scheme III).[22]

Under essentially the same conditions 1- and 2-adamantanol are known to disproportionate quite easily.[6a] However, 1- and 3-homoadamantanol produced neither homoadamantanediols nor homoadamantanones in appreciable quantities. Therefore, the isomerization of the homoadamantyl cations leading to the adamantyl derivatives seems either to be considerably faster than the disproportionation reactions or the disproportionation products are highly unstable. These products, if formed, would generate again the homoadamantyl cations. The bridged 3- and 4-homoadamantyl cations appear to be favored over the corresponding classical cations under the used reaction conditions. However, the 3-homoadamantyl cation obtained in superacid solutions at −78° is stable and does not rearrange.[23] Both ^1H and ^{13}C nmr spectroscopic studies indicate the classical nature of this cation. Therefore, the equilibrium between the classical and the nonclassical 3-homoadamantyl cation should depend strongly upon the reaction conditions. A similar dependence would be expected for the 4-homoadamantyl cation.

Experimental Section

Melting points were determined in sealed capillary tubes using a Thiele apparatus. Infrared spectra were recorded on a Perkin-

Scheme III



Elmer M-257 spectrophotometer, ^1H nmr spectra on a Varian A-60A spectrometer, and mass spectra on a Varian CH-7 mass spectrometer. Purity of compounds was controlled by a Varian Aerograph M-1800 gas chromatograph.

Authentic samples of 1-methyladamantane,[24a] 2-methyladamantane,[24b] 3-homoadamantanol,[14] and 1-adamantylcarbinol[14] were prepared according to the published procedures. Homoadamantane was obtained by catalytic reduction of homoadamantene.[13]

1-Hydroxy-4-homoadamantanone (10).[25] To a stirred mixture of 1-hydroxy-4-adamantanone[6c] (16.6 g, 0.1 mol), KOH (60.0 g, 1.07 mol), water (25 ml), and CH_3OH (150 ml), a solution of "Diazald" (45.0 g, 0.21 mol) in CH_3OH (360 ml) was added dropwise at 0° over a period of 4.5 hr. Stirring was continued overnight at room temperature. The resulting white-gray suspension was evaporated to dryness *in vacuo*, ether (350 ml) and water (250 ml) were added, the layers were separated, and the aqueous one was extracted with ether (7 × 100 ml). Combined ether extracts were dried over $MgSO_4$. The solvent was evaporated to yield 12.4 g (68%) of **10** (≥96% pure by glc): mp 263–265°; ir (KBr) 3400, 2920, 1690 cm^{-1}; mass spectrum m/e (rel intensity) 180 (M^+, 52), 162 (25), 95 (100); tosylhydrazone, mp 156–158°; ir (KBr) 3420, 3230, 2910, 1330, 1170 cm^{-1}.

1-Hydroxy-4-homoadamantanone Ethylene Thioketal (11).[26] To a solution of **10** (3.6 g, 0.02 mol) in ethanedithiol (3 ml) stirred at 0° was added boron trifluoride etherate (1.5 ml). The reaction flask was immediately taken out from the cooling bath and left to stand for about 10 min at room temperature with occasional shaking. Methanol (2–3 ml) was added and the reaction mixture was left overnight in a refrigerator. The precipitate was filtered by suction, washed with cold CH_3OH, and dried: yield 3.9 g (78%); mp 105–107° (recrystallized from CH_3OH); ir (KBr) 3260, 2920, 1445, 1095, 1040 cm^{-1}; mass spectrum *m/e* (rel intensity) 256 (M^+, 100), 196 (77), 105 (43), 95 (43).

1-Homoadamantanol (1). To a solution of **11** (2.7 g, 0.01 mol) in absolute ethanol (60 ml) was added 24 g of Raney nickel (W-2). The mixture was stirred and refluxed for 18 hr. Separated nickel was filtered off and washed with absolute ethanol. The filtrate was concentrated to a small volume, diluted with water (300 ml), and extracted with ether (4 × 80 ml). The extracts were dried and the solvent was evaporated to yield 1.5 g (86%) of 1-homoadamantanol (≥98% pure by glc): mp 266–268° (lit.[15] mp 269–270°); ir (KBr) 3300, 2920, 1450, 1080, 1040, 880 cm^{-1}; mass spectrum *m/e* (rel intensity) 166 (M^+, 33), 95 (100).

Reaction of 1- and 3-Homoadamantanol and 1-Adamantylcarbinol with 75% Sulfuric Acid. General Procedure. A solution of the corresponding alcohol in 75% H_2SO_4 (0.332 g, 0.002 mol in 2.4 ml) was stirred vigorously at 70° for 3 hr. The reaction mixture was shaken occasionally to introduce sublimed hydrocarbons into the solution. In definite time intervals small samples of the reaction mixture were taken out, poured onto plenty of crushed ice, and extracted with ether. The extracts were dried over anhydrous K_2CO_3 and analyzed by glc (SE-30, 90°). After 3 hr the remaining reaction mixture was worked up as described above. The solvent was evaporated to give 0.169 g of the crude product mixture. The main products (**3** and **6**) were isolated by preparative glc (SE-30, 135°) and identified by comparison of their ^1H nmr, ir, and mass spectra with those of authentic samples. The methyladamantanes (**4** and **5**) were identified by glc (SE-30, 90° and FFAP, 100°) using the internal standards. Ir spectra of the crude product mixture showed a very weak absorption corresponding to a carbonyl group (~1700 cm^{-1}); glc analyses indicated no presence of a diol.

A sample of **3**, **4**, and **5** was treated with 75% H_2SO_4 under the same conditions as used in the reactions of **1** and **2**. The glc analyses indicated no reaction.

Acknowledgments. This work was supported in part by a grant from The Research Council of the Republic of Croatia. We thank Professor D. E. Sunko for use of facilities. D. Š. thanks V. T. Š. KoV for understanding.

Registry No. **1**, 31061-64-0; **2**, 14504-80-4; **6**, 770-71-8; **9**, 20098-14-0; **10**, 49701-73-7; **10** tosylhydrazone, 49664-60-0; **11**, 49664-61-1; **12**, 49664-62-2.

References and Notes

(1) E. J. Corey and R. S. Glass, *J. Amer. Chem. Soc.*, **89**, 2600 (1967).
(2) N. V. Averina and N. S. Zefirov, *Chem. Commun.*, 197 (1973).
(3) A. C. Udding, H. Wynberg, and J. Strating, *Tetrahedron Lett.*, 5719 (1968).
(4) B. D. Cuddy, D. Grant, A. Karim, M. A. McKervey, and E. J. F. Rea, *J. Chem. Soc., Perkin Trans. 1*, 2701 (1972).
(5) J. S. Wishnok, P. v. R. Schleyer, E. Funke, G. D. Pandit, R. O. Williams, and A. Nickon, *J. Org. Chem.*, **38**, 539 (1973).
(6) (a) H. W. Geluk and J. L. M. A. Schlatmann, *Tetrahedron*, **24**, 5361 (1968); (b) *Ibid.*, **24**, 5369 (1968); (c) *Recl. Trav. Chim. Pays-Bas*, **90**, 516 (1971).
(7) J. G. Korsloot and V. G. Keizer, *Tetrahedron Lett.*, 3517 (1969).
(8) O. Faulkner and M. A. McKervey, *J. Chem. Soc. C*, 3906 (1971).
(9) 1-Hydroxyadamantan-4-one can be obtained (in a mixture with adamantane-2,6-dione and 1,3-adamantanediol) by the fuming sulfuric acid (20% SO_3) reaction of adamantane followed by chromic acid oxidation.[6c]
(10) At 80° 2-adamantanol undergoes a disproportionation reaction to give adamantanone and adamantane.[6a]
(11) Adamantanone and 1-hydroxy-4-adamantanone are probably formed by disproportionation reactions of the corresponding 2-hydroxyadamantyl derivatives with an adamantyl cation which acts as the hydride acceptor and is converted into adamantane.[6b]

(12) S. H. Liggero, R. Sustmann, and P. v. R. Schleyer, *J. Amer. Chem. Soc.*, **91**, 4571 (1969).
(13) Z. Majerski and K. Mlinarić, *Chem. Commun.*, 1030 (1972).
(14) J. E. Nordlander, S. P. Jindal, P. v. R. Schleyer, R. C. Fort, Jr., J. J. Harper, and R. D. Nicholas, *J. Amer. Chem. Soc.*, **88**, 4475 (1966).
(15) A. G. Yurchenko, F. N. Stepanov, S. S. Isaeva, B. M. Zolotarev, V. I. Kadentsev, and O. S. Chizhov, *Org. Mass Spectrom.*, **3**, 1401 (1970); *Chem. Abstr.*, **77**, 34033t (1972).
(16) 1-Homoadamantanol was also prepared by catalytic reduction of 1-hydroxy-4-homoadamantene (**12**) formed in a poor yield by the reaction of 1-hydroxy-4-homoadamantanone tosylhydrazone with *n*-butyllithium. **12** had mp 250–252°; mass spectrum *m/e* (rel intensity) 164 (M^+, 100), 106 (46), 95 (62); ir (KBr) 3300, 1060, 890, 755, 720 cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.4–1.8 (11 H, m), 2.47 (3 H, broad s), 6.03 (2 H, dd, J = 6.1, 3.5 Hz).
(17) The reproducibility was about ±10% of the reported values; such an error should be expected since the reaction mixtures were heterogeneous.
(18) R. C. Fort, Jr., and P. v. R. Schleyer, *Advan. Alicycl. Chem.*, **1**, 283 (1966).
(19) The exception is, of course, hydride shift between the positions 4 and 5.
(20) Z. Majerski, P. v. R. Schleyer, and A. P. Wolf, *J. Amer. Chem. Soc.*, **92**, 5731 (1970); P. v. R. Schleyer, L. K. M. Lam, D. J. Raber, J. L. Fry, M. A. McKervey, J. R. Alford, B. D. Cuddy, V. G. Keizer, H. W. Geluk, and J. L. M. A. Schlatmann, *ibid.*, **92**, 5246 (1970), and references cited therein.
(21) R. C. Fort, Jr., in "Carbonium Ions," Vol. 4, G. A. Olah and P. v. R. Schleyer, Ed., Wiley-Interscience, New York, N. Y., 1972, Chapter 32, and references cited therein.
(22) This mechanism is supported by an increase of the ratio **5**:**4** with reaction time observed with all three alcohols (**1**, **2**, and **6**). In the very beginning of the reaction this ratio was found to be lower than one in the case of **1** but higher than one in the cases of **2** and **6**.
(23) G. A. Olah and G. Liang, *J. Amer. Chem. Soc.*, **95**, 194 (1973).
(24) (a) E. Osawa, Z. Majerski, and P. v. R. Schleyer, *J. Org. Chem.*, **36**, 205 (1971); (b) Z. Majerski, A. P. Wolf, and P. v. R. Schleyer, *J. Label. Compounds*, **6**, 179 (1970).
(25) *Cf.* P. v. R. Schleyer, E. Funke, and S. H. Liggero, *J. Amer. Chem. Soc.*, **91**, 3965 (1969).
(26) *Cf.* D. Škare and Z. Majerski, *Tetrahedron Lett.*, 4887 (1972).

Synthesis of Unsaturated Azlactones from *N*-Acylamino Acids

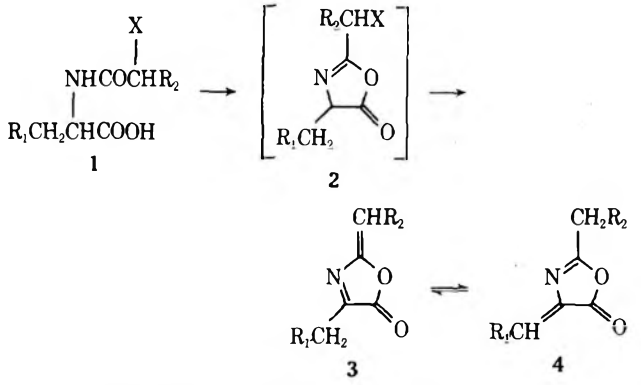
James M. Riordan and Charles H. Stammer*

Department of Chemistry, University of Georgia, Athens, Georgia 30602

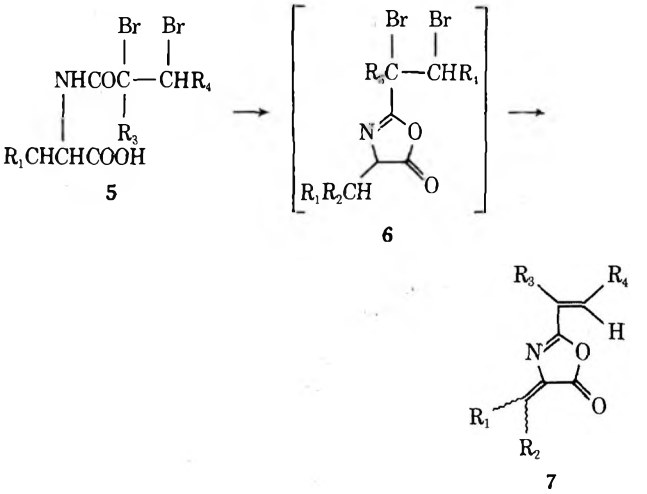
Received August 3, 1973

Phenylalanine, tyrosine, valine, leucine, and isoleucine have been converted to their *N*-(α-methylcinnamoyl) derivatives (**8**). Azlactonization followed by bromine oxidation gave the corresponding unsaturated azlactones (**7**). The configuration about the newly formed double bond was established by nmr correlations, the *Z* configuration being predominant. The mechanism of the double dehydrobromination steps is discussed.

The Bergmann reaction,[1] in which an *N*-(α-haloacyl)-amino acid (**1**) is converted by an acetic anhydride–pyridine mixture into a pseudo-azlactone (**3**), has been known for many years. Several workers[2] have shown that an equilibrium between **3** and the "unsaturated" azlactone **4** can be established and that the position of this equilibrium is determined by the structures of R_1 and R_2 and the conditions[2c,3] under which the reaction is carried out. Our recent communication[4] outlined a procedure making use of an extension of the Bergmann reaction to produce "dehydro" amino acid derivatives without the necessity for equilibration. Treatment of an *N*-α,β-dibromoacylamino acid (**5**) in acetic anhydride at room temperature gave, presumably, the saturated azlactone **6** which was *doubly* dehydrobrominated upon the addition of pyridine to give the unsaturated azlactone **7**. It is the purpose of this paper to describe this work more completely.

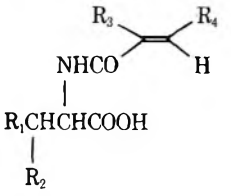


Our initial experiments were carried out on the *N*-(DL-*erythro*-2,3-dibromo-2-methylbutanoyl)-L-phenylalanine (**5a**), which was prepared by a Schotten–Baumann acylation of L-phenylalanine with the dibromoacyl chloride. The derivative, **5a**, was, surprisingly, a sharply melting crystalline solid, even though it was necessarily a mixture of diastereomers. We chose this acyl group because it was readily obtained by bromination of commercially available tiglic acid and we envisioned a necessity for the α-methyl group (R_3 = CH_3) to prevent a possible dehydrobromination of the 2-dibromoalkyl group in **6** since this would, of course, disallow the formation of **7**. A 93% yield[5] of crystalline **7a** was isolated when **5a** was dissolved in acetic anhydride and treated with somewhat more than 2 molar equiv of pyridine. In order to confirm the structure of **7a**, it was prepared by Erlenmeyer[6] condensation of benzalde-



	R_1	R_2	R_3	R_4
a	C_6H_5	H	CH_3	CH_3
b	C_6H_5	H	CH_3	C_6H_5
c	*p*-$AcOC_6H_4$	H	CH_3	C_6H_5
d	CH_3	CH_3	CH_3	C_6H_5
e	CH_3	CH_3CH_2	CH_3	C_6H_5
f	$(CH_3)_2CH$	H	CH_3	C_6H_5
g	C_6H_5	H	H	C_6H_5
h	CH_3	CH_3	H	C_6H_5

Table I
***N*-Acylamino Acids**[a]



8

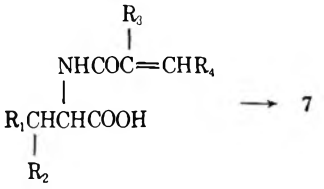
Compd	Mp, °C	Yield,[b] %	Solvent for crystn
8b	154.5–156	90	MeOH–H_2O (1:1)
8c	162–164	72	MEK–petroleum ether (5:1.5)
8f	115–116	87	EtOAc
8d	136–137.5	78	$CHCl_3$–petroleum ether (1:1)
8e	95–99	59[d]	EtOAc–petroleum ether (1:1)
8g[c]	198–199.5	75	MeOH–H_2O (1:1)
8h[c]	187–188	77	EtOAc

[a] Satisfactory analytical data (±0.4% for C, H, N) were reported for all new compounds listed in the table. [b] Yield of recrystallized product. [c] E. Ronwin, *J. Org. Chem.*, **18**, 1546 (1953). [d] Prepared by Mr. Edward Breitholle.

hyde with *N*-tigloylglycine in 26% yield. The identity of these two structures not only established the gross structure of **7a** but gave some insight into its configuration and mechanism of formation in our reaction. The fact that the configuration of the *cis*-2-butenyl group at the 2 position of the azlactone ring was identical in both products indicates that the halogen atoms were eliminated from **6a** in the same trans manner as they were added to the tiglic acid moiety.

When the same sequence of reactions was carried out using DL-leucine, an amorphous unsaturated azlactone was formed. Since we were interested in developing a general method of dehydro amino acid synthesis which would proceed through crystalline intermediates, we changed the acyl group in **5** to the *erythro*-DL-α-methyl-2,3-dibromohydrocinnamoyl function (R_3 = CH_3; R_4 = Ph). Bromination of (*E*)-α-methylcinnamic acid[7] gave the dibromo acid[8] which, after conversion to its acid chloride, was coupled with DL-phenylalanine giving **5b**. Treatment of **5b** with the acetic-pyridine a reagent at room temperature gave the azlactone **7b** in 44% yield. Erlenmeyer synthesis of **7b** in 30% yield from *N*-((*E*)-α-methylcinnamoyl)glycine confirmed the structure of **7b** and again showed that the configurations of both double bonds in the products of these two completely different types of reactions were identical. When the dibromo compound **5b** was also treated with *N*,*N*-dicyclohexylcarbodiimide, a solution of the intermediate saturated azlactone **6b** (C=O absorption, 1830 cm^{-1}) was obtained which afforded **7b** in 62% yield when treated with pyridine. This confirmed the formation of **6b** and its base-catalyzed dehydrobromination to **7b**.

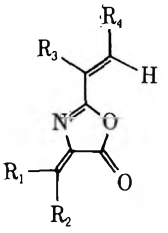
An important simplification of the oxidation procedure was discovered when it was found that a solution of *N*-((*E*)-α-methylcinnamoyl)-DL-phenylalanine (**8b**) in acetic



8

anhydride could be brominated with pyridine perbromide hydrobromide followed by pyridine dehydrobromination to give **7b** in 62% yield. This procedure removed the necessity to prepare the dihaloacylamino acids (**5**) and allowed the unsaturated azlactones to be synthesized directly from the easily prepared α-methylcinnamoylamino acids. Using the appropriate acyl derivatives of tyrosine, valine, isoleucine, and leucine, the azlactones **7c–f** were also prepared. We have subsequently found that the α-methyl group in the cinnamoyl function is unnecessary since the azlactones **7g** and **7h** (R_3 = H) could also be prepared by the direct procedure in acceptable yields. The recrystallized yields and pertinent physical data for the acylamino

Table II
Azlactones[a]

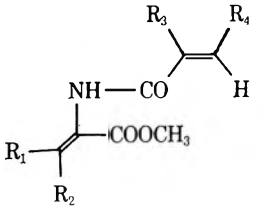


7

Compd	Mp, °C	Yield,[b] %	Solvent for crystn	Nmr, δ
7b	120.5–121	44[c] 62[d]	MeOH–H_2O (3:1)	R_2 = 7.04
7c	163–165	59[d]	Benzene–cyclohexane (3:2)	R_2 = 7.08
7f	83.5–84.5	50[d]	*i*-PrOH	*Z*-R_2 = 6.38 (0.79 H) *E*-R_2 = 6.50 (0.21 H)
7d	138.5–140	63[d]	*i*-PrOH	*Z*-R_1 = 2.32 *E*-R_2 = 2.24
7e	63–67 amorphous	47[d,e]	95% EtOH	*Z*-R_1 = CH_2 = 2.79 R_2 = CH_3 = 2.24 *E*-R_1 = CH_3 = 2.32 R_2 = CH_2 = 2.65
7g	133–134	54[d]	*i*-PrOH	R_2 = 7.08
7h	116–118	24[d]	*i*-PrOH	*Z*-R_1 = 2.30 *E*-R_2 = 2.20

[a] Satisfactory analytical data (±0.4% for C, H, N) were reported for all new compounds listed in the table. [b] Yield after recrystallization. [c] From the dibromoacyl acid. [d] From the cinnamoylamino acid. [e] Prepared by Mr. Edward Breitholle.

Table III
Dehydroamino Acid Methyl Esters[a]



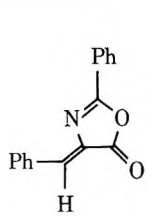
10

Compd	Mp, °C	Yield,[b] %	Solvent for crystn	Nmr, δ
10b	128.5–129.5	83	EtOAc–petroleum ether (2:1)	R_2 = 7.74
10c	109.5–111	52	$CHCl_3$	R_2 = 7.48
(*Z*)-**10f**	108–108.5	77	CCl_4-hexane (1:1)	R_2 = 6.51
(*E*)-**10f**	104–106	57	CCl_4–petroleum ether (1:1)	R_1 = 6.95
10d	98.5–99	93	CCl_4–petroleum ether (1:1)	R_1 = 2.11 R_2 = 1.84
(*Z*)-**10e**	107–108	62[c]	CCl_4–hexane (1:1)	R_1 = CH_2 = 2.49 R_2 = CH_3 = 1.86
(*E*)-**10e**	95–96	73[c]	CCl_4–hexane (1:1)	R_1 = CH_3 = 2.11 R_2 = CH_2 = 2.18
10g	200–201	91	$CHCl_3$–petroleum ether (1:1)	R_2 = 7.73
10h	152–153	82	EtOAc–petroleum ether (3:2)	R_1 = 2.10 R_2 = 1.85

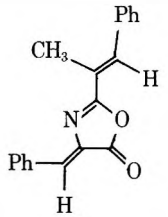
[a] Satisfactory analytical data (±0.4% for C, H, N) were reported for all new compounds listed in the table. [b] Yield after recrystallization. [c] Prepared by Mr. Edward Breitholle.

acids, unsaturated azlactones, and derived esters are reported in Tables I, II, and III, respectively.

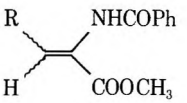
Stereochemistry. The configuration of the new double bond introduced into the carbon chain of the amino acid by the double dehydrobromination reaction should be established if we are to use it later in the synthesis of amino acid derivatives. In 1971, Brocklehurst[9] unequivocally established the *Z* configuration of the 2-phenyl-4-benzylideneazlactone (**9**) prepared by the Erlenmeyer method,



9



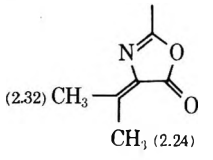
7b



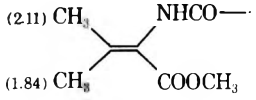
13

using X-ray crystallography. As previously mentioned, the azlactones **7a** and **7b** obtained by our oxidation method were identical with azlactones of the same gross structure prepared by the Erlenmeyer condensation, and should also have the *Z* configuration.[10] Nmr measurements made by Brocklehurst[11a] in 1968, Morgenstern,[10a] and Brown[11b] on the ester **13** derived from both stereoisomers of **9** showed that a vinylic proton cis to the benzamido function in **13** is *downfield* of a proton trans to that function.[12] This key piece of information allowed us to assign the *Z* configuration to azlactones **7a**, **7b**, **7c**, and **7g** and to assign the *Z* configuration to the predominant isomer (79%) of **7f** formed when leucine was oxidized by our procedure. We have no evidence of the formation of more than one isomer when an arylidene azlactone (R_1 = Ar) is the product, but both isoleucine and leucine afforded mixtures of isomers which were separable after conversion to the corresponding methyl esters (**10**) by azlactone methanolysis. Isoleucine gave approximately an equimolar mixture of the *E* and *Z* isomers, while leucine gave a 4:1 *Z*:*E* mixture. This is consistent with the hypothesis that the larger group is favored to take the position cis to the nitrogen atom in the oxazolone ring (*Z* configuration). The *Z* configuration is apparently favored on steric grounds with the larger group taking the least hindered position as discussed by Zimmerman[13] in connection with the Perkin condensation. Isoleucine, having two groups, methyl and ethyl, of approximately the same size, gave about equal amounts of both isomers.

Table IV shows a possible correlation between the change in chemical shift ($\Delta\nu$) of the β-vinylic proton when the azlactone is converted into the corresponding ester and the double bond configuration. Compounds having the *Z* configuration show a smaller downfield shift than those having the *E* configuration in the three cases for which data are available. It may be possible to make assignments on the basis of $\Delta\nu$ as more of these data become available. We can assign the shift positions of the methyl protons in azlactone **7d** and the ester **10d** formed from valine by reference to the elegant work of Brown and Smale,[11b] who deduced the chemical shifts of the methyl protons in methyl α-benzamido-β-methylcrotonate. Referring to the formulas **7d** and **10d**, we see that the $\Delta\nu$ value for

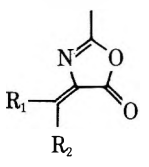


7d



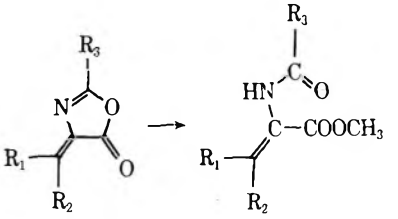
10d

the *Z*-methyl group[14] of **7d** is −0.21 and that of the *E*-methyl group is −0.40. Assuming, then, that an *E*-methyl group[15] will have the larger absolute $\Delta\nu$ value in **7e**, these



7e

Table IV
Correlation of $\Delta\nu$ with Configuration

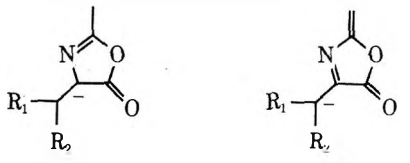


R_1	R_2	R_3	Configuration	$\Delta\nu = \nu_{est} - \nu_{az}$	Ref
3,4-$(CH_3O)_2C_6H_3$	H	C_6H_5	*Z*	0.29[a]	10, 12a
H	3,4-$(CH_3O)_2C_6H_3$	C_6H_5	*E*	0.52[a]	10, 12a
C_6H_5	H	C_6H_5	*Z*	0.20[b]	12a
H	C_6H_5	C_6H_5	*E*	0.32[b]	12a
$(CH_3)_2CH$	H	$C_6H_5CH{=}C(CH_3)$	*Z*	0.08	*c*
H	$(CH_3)_2CH$	$C_6H_5CH{=}C(CH_3)$	*E*	0.40	*c*
Z-CH_3	*E*-CH_3	$C_6H_5CH{=}C(CH_3)$		*Z*-CH_3 −0.21	*c*
				E-CH_3 −0.40	*c*
CH_3[d]	C_2H_5	$C_6H_5CH{=}C(CH_3)$	*E*	−0.21	*c*
C_2H_5[d]	CH_3	$C_6H_5CH{=}C(CH_3)$	*Z*	−0.30	*c*

[a] Ethyl esters. [b] Using the centers of broad peaks. [c] This work. [d] Prepared by Mr. Edward Breitholle.

values can be used to assign the configurations of the two azlactones formed from isoleucine. The isomer of **7e** which shows the larger methyl group $\Delta\nu$ value of −0.30 should be the *Z* isomer ($R_1 = C_2H_5$, $R_2 = CH_3$) and the isomer having $\Delta\nu = -0.21$ can be assigned the *E* configuration ($R_1 = CH_3$; $R_2 = C_2H_5$).

Mechanism. The predominance of *Z* isomers in the products of the bromine oxidation, except in the case of isoleucine where R_1 and R_2 are almost sterically equivalent, indicates that the overall process gives the product having the most stable double bond (*Z* configuration) and is stereoselective rather than stereospecific. Since the 1,4-dehydrobromination should give approximately the same mixture of pseudo-azlactones no matter what the sizes of R_1 and R_2, the second step, which determines the final configuration and *is* sensitive to the bulk of R_1 and R_2, must also be stereoselective and most probably nonconcerted. The first step is very likely to be of the E1cb type,[16] since the carbanion **11** at C-4 in the azlactone ring is of considerable stability as evidenced by the well-known ease of racemization of optically active azlactones.[17] The second step is also likely to be of the same mechanistic type, since the requisite carbanion **12** would have considerable resonance stabilization. The formation of these stable carbanions should lead to thermodynamic control of configuration and an overall stereoselective process.



11 **12**

Experimental Section

General. The nuclear magnetic resonance spectra were recorded on a Varian HA-100 spectrometer with tetramethylsilane as the internal standard and the infrared spectra were obtained on a Perkin-Elmer Model 257 spectrophotometer as Nujol mulls with polystyrene as a standard. Melting points were determined on a Nagle Model Y6 hot stage. Elemental analyses were carried out by Atlantic Microlabs, Atlanta, Ga.

***N*-α-Methylcinnamoyl- and *N*-Cinnamoylamino Acids (8).** A solution of 50 mmol of the acid chloride in 25 ml of 1,2-dimethoxyethane (DME) was added dropwise in 30 min to a solution of 50 mmol of the amino acid in 100 ml of a 1:1 mixture of DME: 1 *N* LiOH in a 300 ml three-necked round-bottomed flask equipped with a magnetic stirrer, delivery funnel, and an electrode attached to a Corning Model 10C pH control unit. The reaction mixture was maintained at pH 10 by the addition of 1 *N* LiOH during the acid chloride addition. After a further 30 min at room temperature, the reaction mixture was cooled with ice and adjusted to pH 1 with concentrated HCl. The white precipitate was filtered, dried *in vacuo* overnight, and purified by crystallization. If a precipitate did not form, the acidic solution was extracted with three 100-ml portions of ethyl acetate, the combined extracts were dried ($MgSO_4$) and evaporated *in vacuo*, and the residue was crystallized.

The yields, melting points, and recrystallization solvents for these *N*-acyl-α-amino acids are given in Table I. Nujol mulls of these acylamino acids showed major absorption bands in the following spectral regions: 1700–1730 (COOH), 1635–1660 (C=C), 1595–1615 cm^{-1} (amide 1).

Azlactones (7). To a solution of 10 mmol of the *N*-acylamino acid in 10 ml of acetic anhydride containing 6 drops of pyridine, 10 mmol of pyridinium hydrobromide perbromide was added. After stirring for 15 min, 3 ml of pyridine was added to the light amber solution and the reaction mixture was stirred for 15 min at room temperature, during which time pyridine HBr precipitated. The mixture was poured into 150 ml of an ice-H_2O mixture, stirred for 30 min, and filtered. The solid obtained was crystallized giving the pure products.

The yields, melting points, recrystallization solvents, and nmr data for these azlactones are given in Table II. Nujol mulls of these azlactones showed major absorption bands in the following spectral regions: 1770–1800 (C=O) with shoulder at 10–20 cm^{-1} lower frequency, 1645–1665 cm^{-1} (C=N).

Dehydro Amino Acid Methyl Esters (10). To a solution of 1 ml of 0.5 *N* sodium methoxide in 50 ml of absolute methanol, 15 mmol of the azlactone was added. After stirring for 30 min at room temperature, the pH of the reaction solution was adjusted to 3 with concentrated HCl. The solvent was evaporated *in vacuo*, the crude residue was dissolved in 50 ml of ethyl acetate, and the solution was extracted with two 25-ml portions of H_2O. The ethyl acetate solution was dried ($MgSO_4$) and evaporated *in vacuo* and the residue was crystallized.

The yields, melting points, recrystallization solvents, and nmr data for these dehydro *N*-acylamino esters are given in Table III. Nujol mulls of these esters showed major absorption bands in the following spectral regions: 1710–1730 (ester C=O), 1650–1660 (C=C), 1615–1645 (C=C), 1600–1625 cm^{-1} (amide 1).

Methyl α-((*E*)-α-Methylcinnamamido)-(*Z*)-β-isopropylacrylate [(*Z*)-10f]. To a solution of 1 ml of 0.5 *N* sodium methoxide in 50 ml of methanol, 2.76 g (10.8 mmol) of crude **7f** was added. After stirring for 15 min at room temperature the pH of the reaction mixture was adjusted to 3 with concentrated HCl. The solvent was evaporated *in vacuo*, giving a crude mixture which was dissolved in 150 ml of ethyl acetate and extracted with two 50 ml-portions of H_2O. The ethyl acetate solution was dried ($MgSO_4$) and evaporated *in vacuo*, giving 2.96 g of a crude mixture of isomers. Crystallization of the mixture from 20 ml of car-

bon tetrachloride and 26 ml of hexane gave 1.91 g (61%) of (*Z*)-**10f**, mp 102–106°. Further recrystallization of (*Z*)-**10f** from 1:1 carbon tetrachloride–hexane gave an analytical sample: mp 108–108.5°; ir (Nujol) 3230 (NH), 1730 ($COOCH_3$), 1655 and 1640 (C=C), 1615 (amide I), 1500 cm^{-1} (amide II); nmr ($CDCl_3$) δ 7.30 [m, 7 H, **PhCH**=C(CH_3)–, NH], 6.51 (d, 1 H, J = 10 Hz, *Z* –CH=C<, 3.72 (s, 3 H, $COOCH_3$), 2.65 [m, 1 H, –C**H**(CH_3)$_2$], 2.11 [s, 3 H, PhCH=C(C**H**$_3$)–], 1.04 ppm [d, 6 H, J = 7 Hz, CH(C**H**$_3$)$_2$].

Methyl α-((*E*)-α-Methylcinnamamido)-(*E*)-β-isopropylacrylate [(*E*)-**10f**]. A 473-mg sample obtained from the mother liquor of (*Z*)-**10f** was chromatographed on a 1.25-cm thick silica gel G plate by elution with $CHCl_3$, giving 214 mg of the crude *E* isomer, which was crystallized from 3:2 CCl_4–petroleum ether (bp 30–60°), yielding 161 mg of (*E*)-**10f**, mp 103–106°. The analytical sample was recrystallized from 1:1 CCl_4–petroleum ether: mp 104–106°; ir (Nujol) 3310 (NH), 1720 ($COOCH_3$), 1655 and 1645 (C=C), 1610 (amide I), 1505 cm^{-1} (amide II); nmr ($CDCl_3$) δ 7.86 (broad s, 1 H, NH), 7.31 [m, 6 H, **PhCH**=C(CH_3)–], 6.95 (d, 1 H, J = 10 Hz, *E* –CH=C<), 3.80 (s, 3 H, $COOCH_3$), 3.31 [m, 1 H, C**H**(CH_3)$_2$], 2.10 [s, 3 H, PhCH=C(C**H**$_3$)–], 1.06 ppm [d, 6 H, J = 7 Hz, CH(C**H**$_3$)$_2$].

Methyl α-((*E*))-α-Methylcinnamamido)-β-methyl-2-pentenorate [(*E*)- **and** (*Z*)-**10e**].[18] To a suspension of 2.55 g (10 mmol) of **7e** in 50 ml of methanol was added 1.01 ml of 0.48 *N* sodium methoxide and in several minutes the solid dissolved. The reaction course was followed by tlc (1:1 *n*-hexane–$CHCl_3$) and the clear solution was acidified with concentrated HCl to pH 2.5. The solvent was evaporated *in vacuo*, the residue was dissolved in ethyl acetate, and the solution was washed with water, dried ($MgSO_4$), and evaporated *in vacuo*, giving 2.9 g (100%) of **10e**. Recrystallization from 1:1 CCl_4–*n*-hexane yielded 2.46 g (86%) of white crystals: mp 82–84°; ir (Nujol) 3275 (NH), 1728 ($COOCH_3$), 1640 (amide I), 1618 cm^{-1} (C=C); nmr ($CDCl_3$) 1.08 (2 t, 3 H, C**H**$_3$CH$_2$), 1.81 (s, 3 H, CH$_3$CH$_2$(C**H**$_3$)C=), 2.18 [s, 3 H, PhCH=C(C**H**$_3$)–], 2.15–2.6 (m, 2 H, CH_2), 3.68 (s, 3 H, $COOCH_3$), 7.30 (s, 5 H, Ph), 7.38 (s, 1 H, PhC**H**=), 7.97 ppm (m, 1 H, NH).

A 600-mg sample of the above product was separated by preparative chromatography using 2.5-mm silica gel plates eluted with 8.5:1.5 *n*-hexane–acetone. The plates were developed 13 times yielding two bands at R_f 0.40 and 0.45. Crystallization from 1:1 CCl_4–*n*-hexane yielded 219 mg of (*E*)-**10e**: mp 95–96°; ir (Nujol) 3238 (NH), 1712 ($COOCH_3$), 1640 (amide I), 1614 cm^{-1} (C=C); nmr ($CDCl_3$) 1.00 (t, 3 H, C**H**$_3$CH$_2$), 2.11 [s, 6 H, PhCH=C(C**H**$_3$)–, CH$_3$CH$_2$(C**H**$_3$)C=], 2.18 (q, 2 H, CH_2), 3.69 (s, 3 H, $COOCH_3$), 7.30 (s, 5 H, Ph), 7.34 (s, 1 H, PhC**H**=), 7.52 ppm (m, 1 H, N**H**), and 180 mg (*Z*)-**10e**: mp 107–108°; ir (Nujol) 3220 (NH), 1717 ($COOCH_3$), 1637 (amide I), 1612 cm (C=C); nmr ($CDCl_3$) 1.11 (t, 3 H, C**H**$_3$CH$_2$), 2.49 (q, 2 H, CH_2), 1.86 [s, 3 H, PhCH=O(C**H**$_3$)–], 2.12 [s, 3 H, CH$_3$CH$_2$(C**H**$_3$)C=], 3.72 (s, 3 H, $COOCH_3$), 7.32 (s, 5 H, Ph), 7.36 (s, 1 H, PhC**H**=), 7.45 ppm (m, 1 H, NH).

N-(DL-*erythro*-2,3-Dibromo-2-methylbutanoyl)-L-phenylalanine (**5a**). A solution of 9.02 g (54.5 mmol) of L-phenylalanine in 150 ml of 10% sodium bicarbonate in a three-necked flask equipped with magnetic stirred and delivery funnel was cooled in an ice bath and 11.75 g (42.5 mmol) of DL-*erythro*-2,3-dibromo-2-methylbutanoyl chloride was added dropwise over a 30-min period. After stirring for 2 hr, the ice bath was removed and the reaction mixture was stirred for another 3 hr at room temperature. The pH of the reaction mixture was adjusted to 1 with concentrated HCl and it was extracted with four 150-ml portions of ethyl ether. The combined extracts were dried (Na_2SO_4) and the ether was evaporated *in vacuo*, giving 15.79 g (90%) of crude **5a**. Crystallization of the crude product from ethyl acetate–petroleum ether gave 13.84 g (81%) of **5a**: mp 116.5–117°; ir (Nujol) 3330 (NH), 1715 (C=O), 1655 (amide I), 1554 cm^{-1} (amide II); nmr ($CDCl_3$) δ 1.68 (d, 3 H, C**H**$_3$CHBr–, J = 6 Hz), 1.88 (d, 3 H, C**H**$_3$CHBr–, J = 6 Hz), 1.91 [s, 3 H, –C(C**H**$_3$)Br–], 1.96 [s, 3 H, –C(C**H**$_3$)Br–], 3.20 (m, 4 H, C**H**$_2$Ph), 5.58 (m, 2 H, CH$_3$C**H**Br–), 5.88 [m, 2 H, –C**H**(COOH)–], 7.20 ppm (s, 10 H, Ph). *Anal.* Calcd for $C_{14}H_{17}NO_3Br_2$: C, 41.30; H, 4.21; N, 3.44 Found: C, 41.48; H, 4.24; N, 3.48.

N-**Tigloylglycine.** A solution of 3.28 g (27.8 mmol) of tigloyl chloride (prepared from 5.0 g of tiglic acid using $SOCl_2$) in 20 ml of tetrahydrofuran was added in 2-ml increments to a solution of 6.45 g (86 mmol) of glycine in 100 ml of 10% aqueous sodium bicarbonate solution contained in a separatory funnel. After the reaction was complete the pH was adjusted to 2 with concentrated HCl and the solution was saturated with NaCl and extracted with three 100-ml portions of ethyl ether. The combined extracts were dried (Na_2SO_4) and the ether was evaporated *in vacuo*, giving 2.51 g (58%) of crude product. Crystallization of the crude product from 1:1 $CHCl_3$–CCl_4 gave 1.69 g (67%) of *N*-tigloylglycine: mp 86.5–88°; ir (Nujol) 3420 (NH), 1705 (COOH), 1665 (C=C), 1585 (amide I), 1535 cm^{-1} (amide II); nmr ($CDCl_3$) δ 6.81 (t, 1 H, NH), 6.57 (q, 1 H, vinyl H), 4.08 (d, 2 H, J = 6 Hz, $-CH_2-$), 1.84 (s, 3 H, CH_3-), 1.75 ppm (d, 3 H, C**H**$_3$CH=). *Anal.* Calcd for $C_7H_{11}NO_3$: C, 53.49; H, 7.05; N, 8.91. Found: C, 53.52; H, 7.11; N, 8.91.

N-((*E*)-α-Methylcinnamoyl)glycine. A solution of 4.50 g (25 mmol) of (*E*)-α-methylcinnamoyl chloride in 25 ml of DME was added dropwise over a 1-hr period to a solution of 3.78 g (50 mmol) of glycine in 25 ml of 2 *N* LiOH and 25 ml of DME in a 100-ml three-necked flask equipped with a magnetic stirrer and a delivery funnel. The DME was evaporated *in vacuo* and the pH of the cooled reaction mixture was adjusted to 1 with concentrated HCl and extracted with two 100-ml portions of ethyl acetate. The combined extracts were washed with two 50 ml-portions of H_2O and dried (Na_2SO_4) and the solvent was evaporated *in vacuo*, giving 4.81 g (90%) of *N*-((*E*)-α-methylcinnamoyl)glycine. Crystallization from ethyl acetate gave 4.22 (77%) of white needles: mp 140–141°; ir (Nujol) 3330 (NH), 1755 and 1735 (COOH), 1630 (C=C), 1585 cm^{-1} (amide I); nmr (TFA) δ 8.00–7.60 (broad s, 1 H, NH), 7.58 (s, 1 H, PhC**H**=), 7.37 (s, 5 H, Ph), 4.45 (s, 2 H, $-CH_2-$), 2.21 ppm (s, 3 H, CH_3). *Anal.* Calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.51; H, 6.03; N, 6.44.

N-(DL-*erythro*-α-Methyl-2,3-dibromohydrocinnamoyl)-DL-phenylalanine (**5b**). A solution of 5.43 g (15.9 mmol) of DL-*erythro*-2,3-dibromo-2-methyl-3-phenylpropanoyl chloride in 14 ml of DME was added dropwise in 1 hr to a solution of 4.51 g (32.8 mmol) of DL-phenylalanine in 160 ml of 5% sodium bicarbonate in a three-necked flask equipped with a magnetic stirrer and delivery funnel. After stirring for 1 hr at room temperature, the reaction mixture was cooled, its pH adjusted to 1 with concentrated HCl, and extracted with three 125-ml portions of ethyl ether. The combined extracts were dried (Na_2SO_4) and evaporated *in vacuo*, giving 5.93 g (80%) of **5b** as an amorphous solid. A solution of the amorphous solid in 10 ml of ethyl acetate was added dropwise to a stirred solution of 3000 ml of petroleum ether, giving a white precipitate; mp 161–167°; ir ($CHCl_3$) 3390 (NH), 1730 (COOH), 1670 (amide I), 1500 cm^{-1} (amide II).

Methyl α-(Tiglamido)-*trans*-cinnamate (10a). To a solution of 1 ml of sodium methoxide in 20 ml of absolute methanol 1.36 g (5.99 mmol) of **7a** was added. After stirring for 15 min at room temperature the pH of the solution was adjusted to 2 with concentrated HCl. The solvent was evaporated *in vacuo*, giving a crude mixture which was dissolved in 40 ml of ethyl acetate, and the solution was extracted with two 25-ml portions of H_2O. The ethyl acetate solution was dried ($MgSO_4$) and the solvent was evaporated *in vacuo*, giving 1.46 g (94%) of methyl α-(tiglamido)-*trans*-cinnamate, mp 117–119°. Crystallization from 1:2 ethyl acetate–petroleum ether gave 1.36 g (88%) of an analytical sample: mp 117.5–119°; ir (Nujol) 3230 (NH), 1710 ($COOCH_3$), 1658 (C=C), 1620 (amide I), 1488 cm^{-1} (amide II); nmr ($CDCl_3$) δ 7.50 (s, 1 H, PhCH=), 7.26 (m, 6 H, **PhCH**=, NH), 6.46 (q, 1 H, J = 7 Hz, CH_3C**H**=), 3.70 (s, 3 H, $COOCH_3$), 1.81 [s, 3 H, CH_3CH=C(C**H**$_3$)–], 1.72 ppm (d, 3 H, J = 7 Hz, C**H**$_3$CH=). *Anal.* Calcd for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.63; H, 6.66; N, 5.33.

2-(*cis*-2-Butenyl)-4-benzylidene-2-oxazolin-5-one (**7a**). **A. From** *N*-(DL-*erythro*-2,3-Dibromo-2-methylbutanoyl)-L-phenylalanine (**5a**). Pyridine (15 ml) was added to a solution of 6.17 g (15.1 mmol) of **5a** in 95 ml of acetic anhydride. After stirring for 30 min at room temperature, the reaction mixture was filtered and poured into 250 ml of anhydrous ethyl ether. The slurry was filtered and the filtrate was evaporated *in vacuo*, giving 4.67 g of an amorphous solid. Crystallization from 5:1 methanol–water gave 3.18 g (93%) of **7a**, mp 115–116°. Recrystallization from methanol–water gave an analytical sample: mp 116–116.5°; ir (Nujol) 1785 (C=O), 1650 (C=N), 1620 cm^{-1} (C=C); nmr (CCl_4) δ 8.02 (m, 2 H, ortho H's of Ph), 7.32 (m, 3 H, Ph), 6.96 (s, 1 H, =CHPh), 6.83 (q, 1 H, J = 6.5 Hz, CH_3C**H**=), 2.04 [s, 3 H, –(CH_3)C=], 1.90 ppm (d, 3 H, J = 6.5 Hz, C**H**$_3$CH=). *Anal.* Calcd for $C_{14}H_{13}NO_2$: C, 73.99; N, 5.77; N, 6.16. Found: C, 74.07; H, 5,83; N, 6.20.

B. From *N*-**Tigloylglycine.** A solution of 550 mg (3.5 mmol) of *N*-tigloylglycine, 200 mg (2.44 mmol) of fused sodium acetate, 550 mg (5 mmol) of benzaldehyde, and 6 ml of acetic anhydride was refluxed for 2 hr. The solvent was evaporated *in vacuo*, giving an amorphous solid which was washed with 5% sodium bicarbonate

and water and crystallized from 6:1 methanol–water giving 417 mg (52%) yellow solid, mp 103–114°. Recrystallization from methanol–water gave 208 mg (26%) of **7a**, yellow needles, mp 116–117°, identical in all respects with product obtained by method A.

C. From *N*-Tigloyl-DL-phenylalanine (8a). A 1.31-g (4.12 mmol) portion of pyridine hydrobromide perbromide was added to a solution of 1.02 g (4.12 mmol) of **8a** in 20 ml of acetic anhydride containing 1 drop of pyridine. The solution was stirred until the reddish-brown solution turned canary yellow. Pyridine (3 ml) was added and the reaction mixture was stirred for 15 min at room temperature. The slurry was poured into 200 ml of ice and H_2O and the mixture was stirred for 30 min and filtered. The precipitate was dried *in vacuo* and the brown solid was crystallized from 1:2 ethyl acetate–petroleum ether, giving 0.63 g (68%) of **7a**, mp 114–115°. Recrystallization from isopropyl alcohol gave 0.50 g (50%) of **7a**, mp 116–116.5°, identical in all respects with product obtained by method A.

***N*-Tigloyl-DL-phenylalanine (8a).** A solution of 2.49 g (20 mmol) of tigloyl chloride in 20 ml of 1,2-dimethoxyethane (DME) was added dropwise in 30 min to a stirred solution of 1.67 g (40 mmol) of lithium hydroxide and 6.96 g (42 mmol) of DL-phenylalanine in 25 ml of H_2O and 20 ml of DME. The reaction mixture was poured into 100 ml of ice and H_2O and the pH was adjusted to 1 with concentrated HCl. The white precipitate was filtered and dried overnight *in vacuo*, giving 3.90 g (75%) of crude **8a**, mp 132–134°. Crystallization from 1:1 ethyl acetate–petroleum ether gave an analytical sample: mp 132–134°; ir (Nujol) 3320 (NH), 1725 (COOH), 1655 (C=C), 1575 (amide I), 1530 cm^{-1} (amide II); nmr ($CDCl_3$) 7.20 (m, 5 H, Ph), 6.38 (m, 2 H, CH_3CH=, NH), 5.92 (m, 1 H, -CHCOOH-), 3.19, 3.22 (q, 2 H, J = 6 Hz, $PhCH_aH_b$), 1.72 (s, 3 H, CH=CCH_3), 1.68 ppm (d, 3 H, CH_3CH=). *Anal.* Calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66. Found: C, 67.86; H, 6.97; N, 5.77.

Preparation of 2-(*cis*-1-Methylstyryl)-4-benzlidene-2-oxazolin-5-one (7b). Method A. From 5b. 1. Using Acetic Anhydride and Pyridine. Pyridine (8 ml) was added to a solution of 2.72 g (5.8 mmol) of **5b** in 45 ml of acetic anhydride. After stirring for 30 min at room temperature, the reaction mixture was poured into 150 ml of an ice–H_2O mixture, stirred for 30 min, and filtered. The yellow precipitate was washed with H_2O and crystallized from 3:1 methanol–water, giving 0.74 g (44%) of **7b**: mp 120.5–121°; ir (Nujol) 1795 and 1775 (C=O), 1645 cm^{-1} (C=N); nmr ($CDCl_3$) δ 8.02 [m, 2 H, 2,6 H's of Ph (R_1)], 7.55 [q, 1 H, J = 3.5 Hz, PhCH=$C(CH_3)$-], 7.38 [m, 8 H, PhCH=$C(CH_3)$- and Ph]; 7.04 (s, 1 H, PhCH=), 2.30 ppm (d, J = 3.5 Hz, 3 H, CH_3). *Anal.* Calcd for $C_{19}H_{15}NO_2$: C, 78.87; H, 5.23; N, 4.84. Found: C, 78.22; H, 5.18; N, 4.84.

2. Using Dicyclohexylcarbodiimide. A solution of 1.77 g (8.6 mmol) of dicyclohexylcarbodiimide in 20 ml of CH_2Cl_2 was added to a solution of 3.88 g (8.3 mmol) of **5b** in 40 ml of CH_2Cl_2. After the reaction mixture was stirred for 3 hr, the dicyclohexylurea was filtered (1.49 g, 78%) and the infrared spectrum of the filtrate showed 1830 (C=O), 1785 (C=O), 1655 cm^{-1} (C=N). Pyridine (4 ml) was added to this solution, which was stirred for 15 min and evaporated *in vacuo*, giving a light yellow solid. The solid was stirred with 100 ml of H_2O, filtered, and dried *in vacuo* overnight, giving 2.71 g of dicyclohexylurea and **7b.** Crystallization from isopropyl alcohol gave 1.49 g (62%) of **7b**, mp 118–120°, spectrally identical with a sample obtained by method A.

Method B. From *N*-((*E*)-α-Methylcinnamoyl)glycine. A solution of 5.89 g (26.8 mmol) of *N*-((*E*)-α-methylcinnamoyl)glycine, 1.72 g (18.6 mmol) of fused sodium acetate, 3.84 ml (37.0 mmol) of benzaldehyde, and 45 ml of acetic anhydride was refluxed for 2 hr. The solvent was evaporated *in vacuo*, giving an amorphous solid which was washed with 5% sodium bicarbonate, water, and methanol, giving a yellow solid which was crystallized from 5:1.5 methanol–water, giving 2.30 g (30%) of **7b**, mp 119–121°, spectrally identical with a sample obtained by method A.

Method C. From *N*-((*E*)-α-Methylcinnamoyl)-DL-Phenylalanine (8b). To a solution of 690 mg (2.23 mmol) of **8b** in 20 ml of acetic anhydride containing 1 drop of pyridine was added 718 mg (2.24 mmol) of pyridine hydrobromide perbromide. After the reaction mixture was warmed to 80°, it was cooled to room temperature and 4 ml of pyridine was added. The reaction mixture was stirred for 10 min at room temperature, during which time a precipitate formed. The mixture was poured into 100 ml of an ice–H_2O mixture, stirred for 30 min, and filtered. The light yellow solid obtained was crystallized from methanol and H_2O, giving 395 mg (62%) of **7b**, mp 121–121.5°, spectrally identical with a sample obtained by method A.

Registry No. 5a, 49659-60-1; **5b,** 49659-61-2; **7a,** 49659-62-3; **7b,** 49659-63-4; **7c,** 49659-64-5; **7d,** 49659-65-6; **7e** (R, Me *Z* to N), 49659-66-7; **7e** (R, Me *E* to N), 49659-67-8; **7f,** 49659-68-9; **7g,** 49659-69-0; **7h,** 49659-70-3; **8a,** 49659-71-4; **8b,** 49659-72-5; **8c,** 49659-73-6; **8d,** 49659-74-7; **8e,** 49659-75-8; **8f,** 49659-76-9; **8g,** 49659-77-0; **8h,** 49659-78-1; **10a,** 49659-79-2; **10b,** 49659-80-5; **10c,** 49659-81-6; **10d,** 49659-82-7; (*Z*)-**10e,** 49659-83-8; (*E*)-**10e,** 49659-84-9; (*Z*)-**10f,** 49659-85-0; (*E*)-**10f,** 49659-86-1; **10g,** 49659-87-2; **10h,** 49659-83-3; L-phenylalanine, 63-91-2; DL-*erythro*-2,3-dibromo-2-methylbutanoyl chloride, 49659-89-4; *N*-tigloylglycine, 35842-45-6; tigloyl chloride, 35660-94-7; glycine, 56-40-6; *N*-((*E*)-α-methylcinnamoyl)glycine, 49659-92-9; (*E*)-α-methylcinnamoyl chloride, 38449-13-7; DL-*erythro*-2,3-dibromo-2-methyl-3-phenylpropanoyl chloride, 49659-94-1; DL-phenylalanine, 150-30-1; dicyclohexylcarbodiimide, 538-75-0.

References and Notes

(1) M. Bergmann and F. Stern, *Justus Liebigs Ann. Chem.*, **448**, 20 (1926).
(2) (a) J. C. Sheehan and W. E. Duggins, *J. Amer. Chem. Soc.*, **74**, 2475 (1950); (b) Y. Iwakura, F. Toda, and Y. Torii, *Tetrahedron*, **23**, 3363 (1967); (c) W. Steglich and R. Hurmans, *Tetrahedron Lett.*, 383 (1966).
(3) H. Kurita, Y. Chigira, M. Masaki, and M. Ohta, *Bull. Chem. Soc. Jap.*, **41**, 2758 (1968).
(4) J. M. Riordan and C. H. Stammer, *Tetrahedron Lett.*, 4969 (1971).
(5) The crude yields of the azlactones prepared in our work were all 70–90%.
(6) E. Erlenmeyer, Jr., *Justus Liebigs Ann. Chem.*, **337**, 283, 294, 302 (1904).
(7) J. R. Johnson in "Organic Reactions," Vol. 1, R. Adams, Ed., Wiley, New York, N. Y., 1942, p 251.
(8) M. Conrad and W. R. Hodgkinson, *Justus Liebigs Ann. Chem.*, 193, 316 (1878).
(9) K. Brocklehurst, R. P. Bywater, R. H. Plainer, and R. Patrick, *Chem. Commun.*, 632 (1971).
(10) (a) A. P. Morgenstern, C. Schutsi, and W. T. Nauta, *Chem. Commun.*, 632 (1971); (b) K. R. Hanson, R. H. Wightman, J. Stanton, and A. R. Battersby, *ibid.*, 185, (1971).
(11) (a) K. Brocklehurst, H. S. Price, and K. Williamson, *Chem. Commun.*, 884 (1968); (b) A. G. Brown and T. C. Smale, *ibid.*, 1489 (1969).
(12) This was contrary to the earlier assumptions made by Brocklehurst which had led him to make incorrect configurational assignments prior to his X-ray work in 1971.
(13) H. E. Zimmerman and L. Ahramjian, *J. Amer. Chem. Soc.*, **81**, 2086 (1959).
(14) *E*- and *Z*-methyl groups are trans and cis to the nitrogen atom, respectively.
(15) The isomer of **7e** with an *E*-methyl group has the *Z* configuration and, conversely, that having a *Z*-methyl group has the *E* configuration.
(16) D. J. McLennan, *Quart. Rev., Chem. Soc.*, **21**, 490 (1967).
(17) (a) M. Goodman and W. J. McGahren, *Tetrahedron*, **23**, 2031 (1967); (b) M. Goodman and L. Levine, *J. Amer. Chem. Soc.*, **86**, 2918 (1964).
(18) This experiment was carried out by Mr. Edward Breitholle in our laboratories.

Detection and Prevention of Urethane Acylation during Solid-Phase Peptide Synthesis by Anhydride Methods[1,2]

R. B. Merrifield,* Alexander R. Mitchell, and Joan E. Clarke

The Rockefeller University, New York, New York 10021

Received September 20, 1973

Solid-phase synthesis of Leu-Ala-Gly-Val furnished Leu-Ala-Gly-Gly-Val as a by-product when urethane-protected amino acids were coupled by the mixed anhydride method. Synthesis of Gly-Val similarly produced Gly-Gly-Val. Activation of N^{α}-2-(4-biphenylyl)-2-propyloxycarbonylglycine (Bpoc-Gly) with ethyl chlorocarbonate and triethylamine in methylene chloride formed an intermediate that reacted with Val-resin to yield *N*-Bpoc-*N*-(Bpoc-Gly)-Gly-Val-resin. Thus, two glycine residues were added during a single solid-phase cycle. Since Bpoc-Gly-Val-resin was not acylated at the urethane nitrogen by symmetrical or mixed anhydrides of Bpoc-Gly, by Bpoc-Gly activated with dicyclohexylcarbodiimide, or by leucine-*N*-carboxyanhydride, urethane acylation occurred before the activated intermediate was coupled to the Val-resin. A mechanism for this side reaction is proposed that involves disproportionation of a mixed anhydride of Bpoc-Gly to the symmetrical anhydride, and intramolecular rearrangement of the latter to form *N*-Bpoc-*N*-(Bpoc-Gly)-Gly, which is subsequently activated by anhydride interchange. Urethane acylation also occurred with Bpoc-alanine as the protected amino acid, with isobutyl chlorocarbonate as the activating agent, or with *N*-methylmorpholine as the base. Although symmetrical anhydrides rearranged slowly, the rate increased markedly on addition of triethylamine hydrochloride. Rearrangement was dependent on temperature and time of mixed anhydride formation and was undetectable after activation at −15° for 10 min and coupling at −15° for 2 hr. No urethane acylation (<0.1 mol %) was observed during coupling of Bpoc-Gly activated with dicyclohexylcarbodiimide under standard solid-phase conditions.

A solid phase synthesis of the model peptide, L-leucyl-L-alanylglycyl-L-valine, by the mixed anhydride method[3-5] produced an undesired by-product. The new substance, representing over 4% of the total product, did not correspond with any of the di- or tripeptides that might have arisen by incomplete coupling or deprotection reactions. Instead, it resulted from urethane acylation. The by-product was isolated and identified as Leu-Ala-Gly-Gly-Val. Some evidence for the mechanism of the acylation reaction has been obtained and conditions by which it can be avoided have been defined.

Mixed anhydride coupling has been applied in a few instances in solid-phase synthesis[6-8] and symmetrical anhydrides are finding increased use.[9-12] Several side reactions, including urethane acylation, are known to occur during conventional syntheses in solution with mixed carboxylic–carbonic anhydride coupling and have been discussed in a review by Albertson.[13] As far as we know, this is the first time urethane acylation has been recognized to have occurred during a solid-phase synthesis with anhydride activation.

Results and Discussion

The initial observation was made following a synthesis of Leu-Ala-Gly-Val by solid-phase methods[14] in which mixed carboxylic–carbonic anhydrides were used in place of dicyclohexylcarbodiimide for the coupling reactions. The completed tetrapeptide resin was cleaved with HF and the crude product mixture was fractionated directly on a cation-exchange column of an amino acid analyzer as described elsewhere.[15] High loading with the peptide products gave a very large peak for the desired tetrapeptide and allowed a good separation and a sensitive measure of the various peptide by-products present. A typical chromatogram is shown in Figure 1. The peaks were identified and quantitated by comparison with synthetic standards.

Attempts were made to eliminate or reduce the amount of the peptide eluted at 189 min by varying the reaction conditions (Table I). Changes in the amino-protecting group, the washing procedure, and the alkyl group of the chlorocarbonate did not markedly change the quantity of this unknown peptide, although replacing the hydroxymethyl resin by a chloromethyl resin (runs 6 and 7),

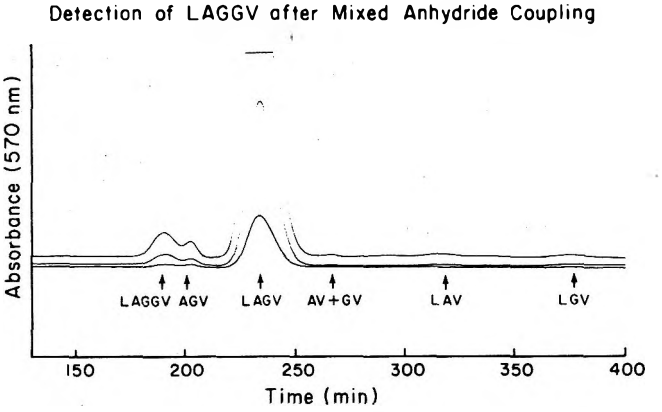


Figure 1. Detection of Leu-Ala-Gly-Gly-Val (LAGGV) after mixed anhydride coupling. Separation was on the long column (0.9 × 60 cm) of a Beckman 120B amino acid analyzer packed with AA-15 sulfonated copoly(styrene–8% divinylbenzene) beads. Elution was at 56°, 66 ml/hr, with pH 3.49 sodium citrate buffer (0.2 *N*). Peptides were detected by the ninhydrin reaction.

which introduced some quaternary ammonium sites, did cause a moderate increase in the by-product. Examination of the product distribution resulting from these mixed anhydride couplings also shows that, in addition to the unknown peptide at 189 min, appreciably more deletion peptides were formed under these conditions than were formed by DCC couplings. The best conditions for DCC coupling gave less than 0.1% of any of the deletion peptides or of the unknown peptide.

In order to identify the 189-min peptide a preparative run on the same ion-exchange column was made. A portion (80%) of the column effluent was diverted to a fraction collector while the remainder was passed through the ninhydrin analytical system of the analyzer. Hydrolysis and amino acid analysis of the peptide eluted at 189 min gave Gly, 1.97; Ala, 1.00; Val, 1.04; Leu, 0.85. This result suggested that 2 mol of glycine had been added during the first synthetic cycle to subsequently give Leu-Ala-Gly-Gly-Val. This pentapeptide was synthesized by the usual solid-phase method using DCC coupling and shown to elute also at 189 min. Since the isolated by-product from the mixed anhydride synthesis and the pentapeptide stan-

Table I
Peptides Detected after Solid-Phase Synthesis of Leu-Ala-Gly-Val under Various Conditions

Run	Resin derivative[a]	% TFA for deprotections[b]	2-Propanol washes[c]	Activation reagent[d]	Coupling time, min	Peptide products, mol %[e] LAGV (234)	LAV (324)	LGV (385)	AGV (201)	GV + AV (266)	LV (450)	LAGGV (189)
1	$HOCH_2R$	1, 1, 1	−	EtOCOCl	120	89.7	0.0	1.05	3.00	1.87	0.0	4.45
2	$HOCH_2R$	20, 1, 1	−	EtOCOCl	120	91.9	0.37	0.64	1.57	0.27	0.27	4.98
3	$HOCH_2R$	20, 1, 1	+	EtOCOCl	120	91.4	0.43	0.54	2.19	0.43	0.0	4.02
4	$HOCH_2R$	20, 1, 1	−	EtOCOCl	5	89.2	0.0	2.09	2.74	0.23	0.0	5.82
5	$HOCH_2R$	20, 1, 1	−	Bu^tOCOCl	120	92.4	0.0	0.48	2.20	0.0	0.0	4.89
6	$ClCH_2R$	20, 1, 1	+	EtOCOCl	120	87.9	0.0	0.22	2.10	1.72	0.0	8.09
7	$ClCH_2R$	20, 1, 1	+	EtOCOCl	120	90.5	0.0	0.50	2.23	0.23	0.0	6.54
8	$ClCH_2R$	20, 1, 1	+	DCC	120	98.7	0.25	0.0	0.82	0.18	0.0	0.0
9	$ClCH_2R$	10, 10, 10	+	DCC	120 × 2	99.8	0.00	0.09	0.08	0.05	0.00	0.00

[a] R represents a copoly(styrene–1% divinylbenzene) bead. The hydroxymethyl resin was esterified by the *N,N'*-carbonyldiimidazole method with Bpoc-Val for run 1 and with Boc-Val for runs 2–5. The chloromethyl resin was esterified by the triethylamine method with Boc-Val for runs 6–8 and with Bpoc-Val for run 9. [b] Percentage of TFA in CH_2Cl_2 used in the three deprotection steps of the syntheses; Boc was removed by 20% TFA and Bpoc by 1% TFA except for run 9, in which 10% TFA was used for removal of the Bpoc group. [c] Three washes with 2-propanol were inserted between the standard CH_2Cl_2 washes following the deprotection, neutralization, and coupling steps. [d] Mixed anhydrides were prepared by treating 1.0 equiv of Bpoc-amino acid with 0.9 equiv of chlorocarbonate and 1.0 equiv of triethylamine in CH_2Cl_2 at 0° for 30 min. [e] Separated on the long column (0.9 × 60 cm) of AA-15 sulfonated polystyrene on a Beckman 120 B amino acid analyzer. A sample containing about 1.4 μmol of total peptides was applied in 1.0 ml of buffer and eluted at 56° with pH 3.49 citrate buffer at 66 ml/hr. The elution time in minutes for each peptide is shown in parentheses, expressed as mole per cent of the ninhydrin-positive free peptides after correction for color constants. Blocked peptides, such as those resulting from wrong-way addition, would not be detected.

Table II
Separation of Peptide Standards on the Amino Acid Analyzer[a]

Compd	Elution time, min
Gly	74
Val	98
Gly-Gly-Gly-Gly-Gly-Gly	128
Gly-Gly-Gly-Gly-Gly	144
Gly-Gly-Gly-Gly	161
Gly-Gly	176
Gly-Gly-Gly	194
Gly-Gly-Val	218
Gly-Val	268

[a] 0.9 × 60 cm Beckman AA-15 column, sodium citrate buffer, pH 3.49, 0.2 *N*, 66 ml/hr, 56°.

Table III
Effect of Temperature and Time on the Formation of Gly-Gly-Val from Val-Resin and the Mixed Anhydride of Bpoc-Gly and EtOCOCl

Run	Activation Temp, °C	Activation Time, min	Coupling[a] temp, °C	% of Gly coupled	Mol % of free peptides Gly-Val	Gly-Gly-Val
1	0	10	25	85	99.7	0.26
2	0	120	25	71	97.5	2.5
3[b]	0	120	25	54	98.2	1.8
4	0	120	0	64	98.5	1.5
5	0	1440	25	30	10.0	90.0
6	0	2880	25	26	7.0	88.8[c]
7	25	1440	25	1.5	48	52
8	−15	10	−15	42	100.0	0.0

[a] Coupling time was 2 hr. [b] Et_3N was replaced by *N*-methylmorpholine. [c] In addition to the di- and tripeptides, 2.5% of Gly-Gly-Gly-Val and 1.8% of Gly-Gly-Gly-Gly-Val were found.

dard were found to be indistinguishable when cochromatographed, it was concluded that the by-product of the synthesis was Leu-Ala-Gly-Gly-Val.

For further study of the side reaction leading to the incorporation of two glycine residues during the single glycine coupling step, the system was simplified by examining only the glycine coupling reaction. The appropriate standard peptides, Gly-Val, Gly-Gly-Val, Gly-Gly, Gly-Gly-Gly, and Gly-Gly-Gly-Gly, were shown to be separable from each other and from glycine and valine on the analyzer column (Table II). Synthesis of Gly-Val by the mixed anhydride method with ethyl chlorocarbonate and triethylamine produced appreciable amounts of Gly-Gly-Val.

For convenience and comparison with DCC experiments, the initial couplings were carried out at 25° in the presence of 5 equiv of Val-resin. Under these conditions the total yield of peptides and the proportion of Gly-Gly-Val were functions of the temperature and time of activation before addition of the Val-resin (Table III). Thus, activation at 0° for 10 min gave only 0.26% Gly-Gly-Val, but the by-product increased to 2.5% in 2 hr and to 90% in 24 hr. The overall yield of coupling decreased from 85% after 10 min to 30% after 24 hr at 0°. When the anhydride solution was held for 24 hr at 25° prior to coupling the yield dropped to only 1.5%. Formation of the anhydride at 0° for 2 hr and coupling at 0° instead of 25° decreased the yield of by-product only slightly. When the synthesis was conducted under more nearly standard conditions for the mixed anhydride method (activation at −15° for 10 min and coupling at −15° for 2 hr) there was no detectable Gly-Gly-Val (<0.1%). The overall yield, however, was only 42%, suggesting incomplete activation[16] or wrong-way addition.[13] Substitution of *N*-methylmorpholine for triethylamine only reduced the yield of Gly-Gly-Val from 2.5% to 1.8% when the activation was for 2 hr at 0°.

When 1.0 mmol of Bpoc-Gly was activated for 48 hr at 0° and then coupled to Val-resin (run 6, Table III), 0.009 mmol of Gly-Val and 0.116 mmol of Gly-Gly-Val were found. In addition, 0.0033 mmol of Gly-Gly-Gly-Val and 0.0024 mmol of Gly-Gly-Gly-Gly-Val were also observed. These peptides accounted for 26% of the starting Bpoc-Gly. In a separate experiment, the filtrate from the coupling reaction was treated with TFA (to deprotect Bpoc-containing components) and found by ion-exchange chromatography to contain 0.007 mmol of Gly, 0.030 mmol of Gly-Gly, 0.004 mmol of Gly-Gly-Gly, and 0.002 mmol of Gly-Gly-Gly-Gly. Thus, 8.7% of the initial Bpoc-Gly was found as free, uncoupled peptides. In addition, 18% of the original Bpoc-Gly was found in the acid-treated filtrate in the form of a ninhydrin-negative product, which was assumed to have been the diketopiperazine derived from 1,4-di-Bpoc-piperazine-2,5-dione by analogy with the results of Zaoral and Rudinger.[17] When the filtrate was subjected to gas chromatography,[18,19] the presence of a

Table IV
Formation of Gly-Gly-Val during Symmetrical Anhydride or Standard DCC Couplings

Run	Activation: Temp, °C	Activation: Time, min	$Et_3N \cdot HCl$	Coupling method	Yield, %[a]	Peptide products,[b] mol %: Gly-Val	Peptide products,[b] mol %: Gly-Gly-Val
1	25	10	−	SA[c]	100	100.0	0.0
2	25	120	−	SA[c]	70	100.0	0.0
3	25	1440	−	SA[c]	24	96.5	3.3
4	25	120	+	SA[c]	65	91.4	8.6
5	25	1440	+	SA[c]	45	84.5	15.2
6	0°	120	+	SA[c]	81	93	7
7	25°	120	−	SA[d]	62	99.7	0.34
8			−	DCC[e]	100	100.0	0.0
9			+	DCC[e]	100	99.8	0.24

[a] The yield of the symmetrical anhydride (SA) runs is based on the theoretical amount of anhydride that could be formed; if based on Bpoc-Gly, it would be $^1/_2$ of the values shown. The yield of the DCC runs is based on the Val-resin, which is limiting; if based on the excess Bpoc-Gly the values would be $^1/_4$ of those shown. [b] After coupling, the peptides were cleaved from the resin with HF containing 10% anisole at 0° for 1 hr. The crude mixture was extracted from the resin and fractionated on an ion-exchange column (0.9 × 60 cm, pH 3.49 citrate). [c] Bpoc-Gly (1 equiv) was activated with 0.5 equiv of DCC in CH_2Cl_2 either without or with 1 equiv of $Et_3N \cdot HCl$. Val-resin (2 equiv) was then added and coupling was continued for 2 hr at 25°. [d] Boc-Gly (1 equiv) was activated with DCC (1 equiv) in CH_2Cl_2 for 2 hr and then coupled with Val-resin (3 equiv) for 2 hr at 25°. [e] Bpoc-Gly (4 equiv) was added to Val-Resin (1 equiv) in CH_2Cl_2 and stirred for 10 min either without or with 4 equiv of $Et_3N \cdot HCl$. DCC (4 equiv) was then added and coupling was continued for 2 hr at 25°.

component which cochromatographed with an authentic sample of glycine diketopiperazine was demonstrated.

Urethane acylation is not limited to glycine, although it probably proceeds faster with the unhindered amino acid. For example, treatment of Bpoc-Ala with EtOCOCl and Et_3N for 25 hr at 0°, followed by coupling with Val-resin, gave a low yield of a peptide mixture composed of 14% Ala-Ala-Val and 86% Ala-Val.

Several other coupling methods were examined to determine whether or not the side reaction is limited to the mixed anhydride procedure. The symmetrical anhydride, $(Bpoc\text{-}Gly)_2O$, was prepared by treating Bpoc-Gly with 0.5 equiv of DCC in CH_2Cl_2. After various times at 0° or 25° the reagent was mixed with excess Val-resin and allowed to couple for 2 hr at 25°. In separate runs, 1 equiv of $Et_3N \cdot HCl$ was added to simulate the amount of this salt formed during a mixed anhydride coupling. Finally, a conventional DCC coupling was examined for comparison. In this experiment 4 equiv of Bpoc-Gly and 1 equiv of Val-resin were mixed and stirred for 10 min at 25° either with or without 4 equiv of $Et_3N \cdot HCl$. Then 4 equiv of DCC was added and coupling was continued for 2 hr at 25°. The results of these experiments are summarized in Table IV. In the absence of $Et_3N \cdot HCl$ the symmetrical anhydride produced no Gly-Gly-Val in 10 min or 2 hr and only 3.3% after 24 hr at 25°. The presence of $Et_3N \cdot HCl$ caused a marked increase, however, and even at 0° for 2 hr 7% Gly-Gly-Val was formed (compare run 6, Table IV with run 2, Table III). The standard DCC coupling gave no detectable Gly-Gly-Val (0.1%), but 0.24% was found when 4 equiv of $Et_3N \cdot HCl$ was present.

When 0.53 mmol of Boc-Gly was treated with 0.53 mmol of DCC for 2 hr at 25°, and the CH_2Cl_2-soluble fraction was deprotected with TFA and dissolved in water, the product consisted of a mixture of 0.24 mmol of Gly and 0.12 mmol of Gly-Gly. Since the starting material was free of Gly-Gly derivatives, it was concluded that the intermediate isourea, or symmetrical anhydride–DCC complex, underwent an acylation reaction at the urethane nitrogen in a manner analogous to that reported by De Tar, *et al.*,[20] for the benzyloxycarbonyl derivative. When 0.53 mmol of Boc-Gly was treated with 0.53 mmol of DCC for 2 hr at 25° as before, and then was treated with excess Val-resin, the resin-derived product consisted of a mixture of 0.16 mmol of Gly-Val and 0.0005 mmol of Gly-Gly-Val. These data are consistent with the view that essentially all of the Gly was still present as the reactive symmetrical anhydride after 2 hr. On the other hand, only a trace (0.4%) of the rearranged Gly-Gly product produced during the activation period was in activated form that could couple with the added Val-resin. This can be rationalized best in terms of the intramolecular mechanism to be discussed later and argues against a mechanism in which the Boc-glycyl isourea would acylate itself by an intermolecular pathway. When DCC was added to Boc-Gly that was already in the presence of Val-resin and the mixture was allowed to couple for 2 hr at 25°, no Gly-Gly-Val was produced.

Evidence for the structure of the resin-bound product leading to Gly-Gly-Val was obtained by comparing the number of Bpoc groups with the amino acid composition. The mixed anhydride was prepared by incubating 19.3 μmol of Bpoc-Gly with equivalent amounts of EtOCOCl and Et_3N in CH_2Cl_2 at 0° for 24 hr. An excess (112 μmol) of Val-resin was added and coupling was continued for 2 hr at 25°. The thoroughly washed resin was deprotected by treatment with 1% TFA in CH_2Cl_2. The increased absorbance of the TFA solution at 261 nm due to 2-(4-biphenylyl)propene (ϵ 1.74 × 10^4) corresponded to 7.60 μmol of Bpoc groups. Subsequent HF cleavage of the resin and chromatographic analysis of the resulting peptides revealed the presence of 0.34 μmol of Gly-Val, 3.39 μmol of Gly-Gly-Val, and 87.3 μmol of free Val. Assuming that 0.34 μmol of Bpoc was bound to the Gly-Val, then 7.26 μmol of Bpoc was bound to 3.39 μmol of Gly-Gly-Val (ratio 2.11:1). This indicates clearly that the protected resin-bound tripeptide contained two Bpoc groups for every Val residue, or an average of one Bpoc per Gly residue. The data are consistent with structure I. *N*-biphenylisopropyloxycarbonyl-*N*-(biphenylisopropyloxycarbonylglycyl)glycylvalyloxymethyl resin.

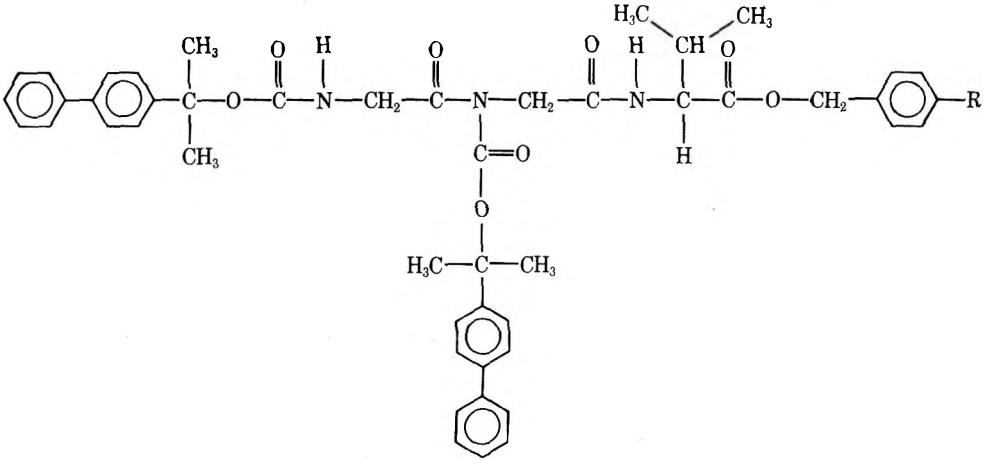
On the Mechanism of the Reaction. Four mechanisms have been considered to explain the appearance of additional amino acid residues in peptides from solid-phase syntheses in which anhydride methods were used.

A. Acylation of the Amide Nitrogen of Bpoc-Gly-Val-Resin and Insertion. Brenner[21] has proposed that net insertion of an amino acid can be effected through N-acylation of an amide bond of a peptide backbone by an activated N-protected amino acid followed by intramolecular cyclization and ring opening. Mitchell and Roeske[22] detected no triglycine, however, on treating Boc-Gly-Gly-resin with 10 equiv each of Boc-Gly and DCC followed by deprotection in acid and treatment with triethylamine. The same experiment was repeated in this study, using mixed anhydride activation of Boc-Gly, and no formation

Table V
Stability of Amide and Urethane Nitrogen Atoms toward Several Acylating Agents

No.	Amide or urethane component	Acylating agents (activating conditions)	Reaction time, hr	—Products, mol %[a]— Starting material	Acylated product	Ref
1	Boc-Gly-Val—R[b] 1 equiv	Boc-Gly + EtOCOCl + Et_3N (30 min, 0°) 4 equiv 4 equiv 4 equiv	2	100	0	*c*
2	Boc-Gly-Val—R 1 equiv	Boc-Gly + DCC (10 min, 25°) 4 equiv 2 equiv	2	100	0	*c*
3	Boc-Gly-Val—R 1 equiv	Boc-Gly + DCC 4 equiv 4 equiv	2	100	0	*c*
4	Boc-Gly-Val—R 1 equiv	Leucine *N*-carboxyanhydride 10 equiv	24	100	0	*c*
5	Z-NH$(CH_2)_5$C(=O)—R 1 equiv	Boc-Gly + Bu^{t}OCOCl + Et_3N (15 min, −10°) 86 equiv 81 equiv 86 equiv	12	100	0	*c*
6	Z-NH$(CH_2)_5$C(=O)—R 1 equiv	Boc-Gly + DCC (10 min, 25°) 81 equiv 81 equiv	12	100	0	*c*
7	Boc-Gly-Gly—R 1 equiv	Boc-Gly + Bu^{t}OCOCl + Et_3N (15 min, −10°) 68 equiv 64 equiv 68 equiv	2	100	0	*c*
8	Boc-Gly-Gly—R 1 equiv	Boc-Gly + DCC 10 equiv 10 equiv	24	100	0	14
9	Z-NHCHRC(=O)-NH_2	Z-NHCHRCOOH + EtOCOCl + Et_3N			0	23
10	Z-Ala-NH_2	Z-Gly-Cl			0	23

[a] Products from runs 1–6 were separated and quantitatively measured on the amino acid analyzer following deprotection and cleavage from the resin by HF or HBr. After the attempted acylation reaction in runs 7 and 8, the peptide resin was deprotected with TFA, treated with 10% Et_3N–CH_2Cl_2, and then cleaved with HBr. A portion of the peptide resin from run 1 was similarly treated and no acylated product was detected. Limit of detection was 0.1 mol %. [b] R represents oxymethylcopoly(styrene–1% divinylbenzene). [c] This study.



I

of triglycine was observed. Similarly, treatment of Bpoc-Gly-Val-resin with Bpoc-Gly-OCO_2Et did not lead to the formation of Gly-Gly-Val (Table V). These results support the original contention[22] that the Brenner mechanism is not a significant side reaction during solid-phase peptide synthesis.

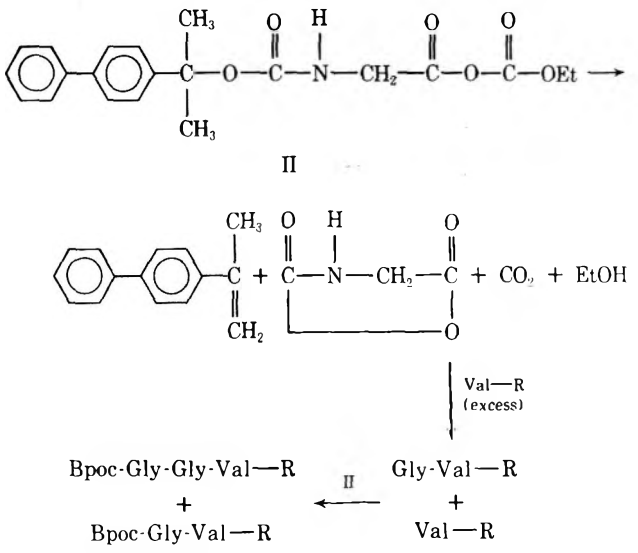
In the context of amide reactivity, Antonov and Shemyakin[24] studied the reaction of protected peptide esters with acylating agents of higher reactivity than those used in the present study. Phthalylglycyl chloride was found to acylate not the amide nitrogen, but the urethane nitrogen of *N*-benzyloxycarbonyl dipeptide esters. Acylation of the peptide bond in a phthalyl dipeptide ester was effected through the use of a more potent acylating agent, azidoacetyl chloride, at reflux in toluene for several hours. In light of the nonreactivity of amide nitrogens toward the less active acylating agents (Table V) it is interesting that Fankhauser, *et al.*,[25] have recently described a model system in which amide acylation (and subsequent insertion) was thought to have occurred during solid-phase peptide synthesis. It appears, however, that other interpretations of their data are possible.

B. Acylation of the Urethane Nitrogen of Bpoc-Gly-Val-Resin. This mechanism involves coupling of activated Bpoc-Gly to Val-resin and N-acylation of the urethane bond of the resulting Bpoc-Gly-Val-resin by a second equivalent of activated Bpoc-Gly. However, the effects of temperature and activation time of the mixed anhydride indicated that the side reaction was occurring in solution during the activation step rather than after the coupling reaction between Boc-Gly-OCO_2Et and Val-resin. This conclusion was confirmed by treatment of Boc-Gly-Val-resin with excesses of Boc-Gly-OCO_2Et, $(Boc\text{-}Gly)_2O$, Boc-Gly + DCC, or leucine *N*-carboxyanhydride. No Gly-Gly-Val or Leu-Gly-Val was obtained (Table V), indicating that the urethane nitrogen was not acylated under these conditions. Attempts to acylate the urethane bond of 6-(benzyloxycarbonylamino)hexanoyl resin with large ex-

cesses of Boc-Gly-OCO_2Bu[1] or Boc-Gly + DCC were also unsuccessful.

C. Acylation of the Amino Nitrogen *via* an *N*-Carboxyanhydride. Bodanszky, *et al.*,[26] recently reported that activation of Boc-amino acids with DCC in CH_2Cl_2 gave rise to a precipitate that contained ninhydrin-positive material. They pointed out that intermediate Boc-amino acyl isourea contains a good anionic leaving group and a potential cation of high stability and that the presence of two oppositely polarized centers in such a molecule favors the formation of an *N*-carboxyanhydride (NCA) which, following hydrolysis, could account for the ninhydrin-positive product. By this reasoning Bpoc-Gly anhydride (or Boc-Gly anhydride) should also form the NCA and subsequently give rise to Gly-Gly-Val as shown in Scheme I. Thus, if a small amount of NCA were to form it would react rapidly with the large excess of Val-resin to produce a mixture of Gly-Val-resin and Val-resin (very little polyglycyl-valine-resin would be expected from an NCA•polymerization process because of the excess amine initiator). The remaining Bpoc-Gly mixed anhydride would then react to give Bpoc-Gly-Val-resin and Bpoc-Gly-Gly-Val-resin. By this mechanism the resin-bound tripeptide would contain Bpoc and Val in a ratio of 1:1. However, it was found (run 6, Table III) that the ratio was 2.11:1.

Scheme I
The *N*-Carboxyanhydride as a Possible Intermediate Leading to Gly-Gly-Val



During the activation and incubation steps, before addition of the Val-resin, an appreciable amount of NCA should have accumulated if this were the mechanism of the side reaction. In an experiment (run 5, Table III) where 27% of the Boc-Gly eventually appeared as Gly-Gly-Val, no carboxyanhydride could be found by infrared spectroscopy. As little as 5% of Gly NCA would have been detected by its characteristic absorption at 1857 cm^{-1}. Thus Gly NCA did not accumulate during the activation step and does not appear to be on an important route to the observed Gly-Gly-Val.

D. Acylation of the Urethane Nitrogen of Bpoc-Gly Anhydride. The probable mechanism for the formation of *N*-Bpoc-*N*-(Bpoc-Gly)-Gly-Val-resin involves the acylation of the urethane nitrogen of Bpoc-Gly anhydride in solution, followed by coupling of the resulting glycylglycine derivative with Val-resin. The acylation reaction might occur intermolecularly or intramolecularly.

As far as we are aware, this is the first time the urethane acylation reaction has been recognized to have occurred during a solid-phase synthesis, although it is well known to occur during conventional syntheses in solution with mixed carboxylic-carbonic anhydrides. Kopple and Renick[27] found that activation of Z-Gly with ethyl chlorocarbonate and triethylamine for 10 min at −5°, followed by coupling with glycine ethyl ester, gave rise to a 30% yield of a by-product containing two Z-Gly residues per glycine ester. Treatment with HBr–HOAc yielded the linear tripeptide, HBr·Gly-Gly-Gly-OEt. The initial product was deduced to be *N*-Z-*N*-(Z-Gly)-Gly-Gly-OEt. It was assumed that this diacylamide was formed by reaction of the mixed anhydride with glycine ethyl ester and acylation of the resulting Z-Gly-Gly-OEt by another equivalent of the mixed anhydride. Similarly, Schellenberg and Ullrich[28] found 17% of crystalline *N*-Z-*N*-(Z-Gly)-Gly-Glu-$(OEt)_2$ following the coupling of diethyl glutamate with the mixed anhydride of Z-Gly and isobutyl chlorocarbonate. The expected Z-Gly-Glu-$(OEt)_2$ was obtained in 66–71% yield from the filtrates. No mechanism was proposed. Determann[29] treated the reaction product of Z-Phe and ethyl chlorocarbonate with NaOH and isolated 1-benzyloxycarbonyl-3-(2-benzylacetic acid)-5-benzylhydantoin. He concluded that one molecule of the mixed anhydride had undergone an attack by the nucleophilic nitrogen of another molecule in an *inter*molecular acylation to give *N*-Z-*N*-(Z-Phe)-Phe-OCOOEt, which then underwent ring closure in alkali, with loss of benzyl alcohol, to give the hydantoin. Kotake and Saito[30] obtained an 85% yield of *N*-Z-*N*-(Z-Gly)-Gly after treatment of $(Z\text{-}Gly)_2O$ with Et_3N (0.1–1 equiv). The high yield suggests, but does not prove, that the acylation reaction was *intra*molecular.

Urethane acylation is not limited to symmetrical carboxylic anhydrides and mixed carboxylic-carbonic anhydrides. This side reaction was first observed by Wieland and Heinke[31] when Z-Gly was activated by the phosphorous oxychloride method. The product, *N*-Z-*N*-(Z-Gly)-Gly, was obtained in 30% yield.

Neither is the acylation reaction limited to N^{α}-urethane-protected amino acids; Zaoral and Rudinger[17] observed it when the mixed anhydride formed from tosylglycine and *sec*-butyl chlorocarbonate in pyridine was treated with aniline. They actually isolated ten crystalline products from the single reaction mixture, including 15% of *N*-Tos-*N*-(Tos-Gly)-Gly anilide. Several mechanisms for the origin of the observed products were discussed in some detail. One way in which imides such as Tos-$NHCH_2C(=O)$-*N*-Tos-CH_2COOH could arise under the conditions of a mixed anhydride synthesis was *via* an O to N shift that would allow for a mobile equilibrium between Tos-$NHCH_2C(=O)OC(=O)CH_2NH$-Tos and Tos-$NHCH_2C(=O)$-*N*-Tos-CH_2COOH. This process requires first that the symmetrical anhydride be formed by disproportionation of the mixed carboxylic-carbonic anhydride. Indeed, several reactions, all of which were expected to give the symmetrical anhydride $(Tos\text{-}Gly)_2O$, were found to lead invariably to *N*-Tos-*N*-(Tos-Gly)-Gly. Evidence for the existence of both species was obtained when the reaction between Tos-Gly-Cl and Tos-Gly was followed by infrared spectroscopy. They concluded that it was unlikely that disproportionation under the conditions used for the mixed anhydride would be sufficiently extensive to account for all of the imide actually isolated (~56%). In addition, disproportionation requires CO_2 evolution, but they observed none. For these reasons it appeared likely that direct acylation of tosyl-glycine, or more probably of the mixed anhydride, by a second molecule of the mixed anhydride also occurred.

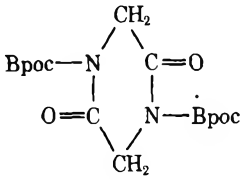
Thus, the widely observed side reaction leading to the incorporation of two residues of glycine instead of only one has been attributed to acylation of the urethane nitrogen

of a protected dipeptide ester,[27] of an N-protected amino acid,[17] or of an N-protected amino acid mixed anhydride[29,31] by intermolecular reactions, or, in part, to acylation of an N-protected amino acid symmetrical anhydride by an intramolecular reaction.[17,30]

Evidence gathered in this study of the side reaction during solid-phase synthesis favors the view that it occurs by an intramolecular rearrangement as outlined in pathway A, Scheme II. Thus, Bpoc-Gly-OCO_2Et (II), first formed in solution from Bpoc-Gly and EtOCOCl, disproportionates to the symmetrical anhydride $(Bpoc\text{-}Gly)_2O$ (III), which undergoes an intramolecular acylation to give *N*-Bpoc-*N*-(Bpoc-Gly)-Gly-OH (IV). This diacyl dipeptide, which is not activated for coupling, would then become activated by an anhydride interchange with other anhydride species present in solution, such as mixed anhydride (II) or symmetrical anhydride (III), to give *N*-Bpoc-*N*-(Bpoc-Gly)-Gly-*O*-Gly-Bpoc (V) or $[N\text{-Bpoc-}N\text{-(Bpoc-Gly)-Gly}]_2O$ (VI), or possibly *N*-Bpoc-*N*-(Bpoc-Gly)-Gly-OCO_2Et (VII). After the activation period, during which these reactions could occur, each of the anhydride species would then couple with the excess Val-resin to give a mixture of Bpoc-Gly-Val-resin (VIII) and *N*-Bpoc-*N*-(Bpoc-Gly)-Gly-Val-resin (I) in proportion to their concentrations. Deprotection and cleavage from the resin by HF would then give the di- and tripeptides finally observed. During the anhydride interchange reactions (*e.g.*, V → VI) additional symmetrical anhydride would be expected to form and would recycle to lead to more of the diacyl dipeptide anhydrides (V, VI, VII).

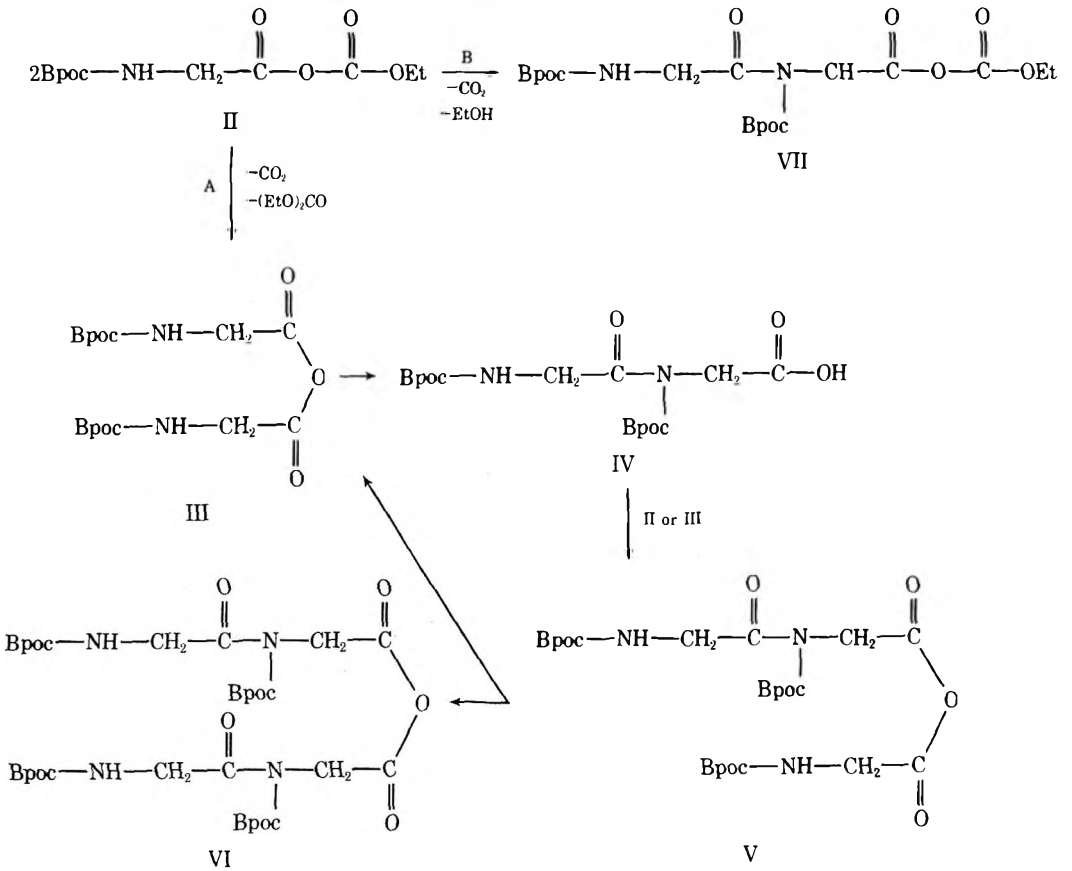
By the symmetrical anhydride route the maximum incorporation of glycine would be 50% if the product were all Gly-Val and, depending on the relative rates of the individual reactions, the maximum yields would be between 33 and 67% if the product were all Gly-Gly-Val. The alternative route (pathway B, Scheme II) would involve the intermolecular generation of VII directly from II. By this route up to 100% of glycine could be incorporated, either as Gly-Val or Gly-Gly-Val. When Bpoc-Gly, EtOCOCl, and Et_3N were incubated at 0° for 24 hr, and then treated with Val-resin, Gly-Val and Gly-Gly-Val were found in a molar ratio of 1:10. The coupling yield based on Bpoc-Gly was 37%. However, the pathway cannot be deduced from yield alone because a complete accounting of materials was not made and side reactions could markedly reduce the overall yield. It is important to note that the amino acid and peptide products observed in this study were detected by the ninhydrin reaction after chromatography. The presence of blocked products resulting from wrong way addition would not be measured by this analytical system.

The diketopiperazine IX is thought to be another inactivation product.[17] It was observed that prolonged standing of an activation solution at 25° led to a very low coupling yield. The filtrate contained a ninhydrin-negative component which gave rise on hydrolysis to a quantity of glycine approximately equal to that which had coupled to Val-resin. The presence of the diketopiperazine was established by gas chromatography.[18,19]

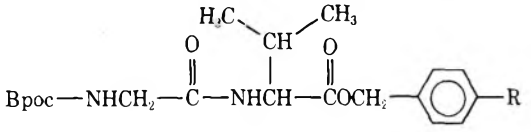


IX

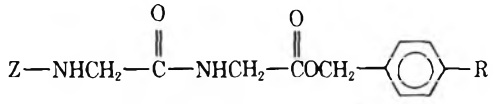
Scheme II
Mechanisms Leading to the Rearrangement Product, Gly-Gly-Val, *via* Urethane Acylation



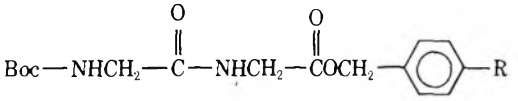
The main reason for rejecting the intermolecular acylation (pathway B) as the major route is the complete lack of reactivity of the urethane nitrogen of resin esters X, XI, and XII with various amino acid anhydrides, including



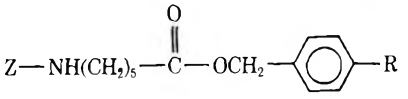
X



XI



XII



XIII

Bpoc-Gly-OCO_2Et, Boc-Gly-OCO_2Bu^i, $(Bpoc\text{-}Gly)_2O$, Bpoc-Gly-*O*-C(=NC_6H_{11})NHC_6H_{11}, and Val-NCA. In addition, large excesses of Boc-Gly-OCO_2-Bu^i or Boc-Gly + DCC were unable to effect acylation of XIII. Moreover, the reaction did not occur in solution between Z-amino acid amides or anilides and mixed anhydrides.[23] It seems unlikely that the urethane nitrogen of Bpoc-Gly-OCO_2Et would be appreciably more reactive toward acylation under these conditons. A greatly enhanced rate, however, could be expected from the *intra*molecular acylation of II to give III (Scheme II).

If pathway A is the actual route for the rearrangement of the mixed anhydride, the symmetrical anhydride should undergo a similar rearrangement at a comparable rate under the same conditions. Since the usual conditions for formation and coupling of symmetrical anhydrides are not the same as for mixed anhydrides, the results cannot be compared directly. Thus, activation of Bpoc-Gly by 0.5 equiv of DCC in CH_2Cl_2 for 10 min or 2 hr at 25°, followed by coupling with Val-resin, gave no Gly-Gly-Val, and activation for 24 hr gave only 3.3% (Table IV), whereas the mixed anhydride produced 2.5% in 2 hr at 0° and 90% after 24 hr (Table III). When 1 equiv of triethylamine hydrochloride was added to simulate the amount of this salt formed during the mixed anhydride reaction,[32] the results were quite different. Then $(Bpoc\text{-}Gly)_2O$ gave rise to 7% Gly-Gly-Val after standing for 2 hr at 0°. Therefore, the data up to 2 hr are compatible with pathway A and support the view that it is the major route to the rearrangement products. The data at longer times are complicated by low yields and undetermined by-products and are more difficult to rationalize.

The normal DCC coupling of Bpoc-Gly with Val-resin gave no detectable tripeptide, and the presence of an additional mole of DCC did not catalyze the side reaction. When $Et_3N\cdot HCl$ was present, however, even the DCC method produced 0.26% of Gly-Gly-Val.

Rearrangement of II should produce CO_2, and it was observed. The activation solution containing Bpoc-Gly + EtOCOCl + Et_3N in CH_2Cl_2 was placed at 25° in a closed cell, then underwent infrared spectroscopy. A strong, sharp peak at 2300 cm^{-1} for CO_2 was observed after 25 min and the peak was approximately twice as large after 4 hr. When the activation was carried out in a flask connected to the air by a drying tube, no CO_2 peak could be found. The infrared data also showed a steady drop in the mixed anhydride carbonyl peak at 1840 cm^{-1} with a half-time of about 45 min. The second anhydride peak at 1760 cm^{-1} decreased but was replaced by an overlapping peak at 1740 cm^{-1} which is attributed to the imide carbonyl resulting from the acylation. The urethane carbonyl peak at 1725 cm^{-1} remained unchanged.

Conclusions

The present experiments show that substantial quantities of by-product can be formed during solid-phase syntheses with the mixed anhydride method at 0°. The undesired product arises by an intramolecular acylation of the urethane nitrogen of Bpoc-glycine during the activation step in solution, rather than by acylation of a resin-bound peptide. The reaction can also occur with other amino acids, although at a slower rate. When the mixed anhydride was formed and coupled at lower temperature (−15°) the urethane acylation could not be detected. Therefore, with respect to *this side reaction*, the mixed anhydride method appears to be satisfactory, even with glycine, for solid-phase peptide synthesis. However, because the conditions are critical, the possibility of adding two residues during a single coupling step must be kept in mind.

The symmetrical anhydride of Bpoc-Gly, generated by DCC, showed far less tendency to undergo the rearrangement than the mixed anhydride. The difference is correlated with the presence of $Et_3N\cdot HCl$ during the formation of the mixed anhydride. In addition, the standard DCC coupling procedure that has been used extensively for solid-phase synthesis produced none of the rearrangement product in these model systems. Thus, urethane acylation represents a side reaction in solid-phase peptide synthesis that can be avoided under appropriate conditions.

Experimental Section

Infrared spectra were taken with a Perkin-Elmer Model 237B grating infrared spectrophotometer. Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Amino acid and peptide analyses were carried out on Beckman amino acid analyzers (Model 120B and 121). Elemental analyses were performed by Mr. S. T. Bella. An F & M Model 402 gas chromatograph was used to determine glycine diketopiperazine as described elsewhere.[18,19] The solvents used for thin layer chromatography (precoated 0.25-*mm* silica gel G plates, Analtech) were 1-butanol–acetic acid–water (BAW) (4:1:1) and chloroform–methanol–acetic acid (CMA) (17:2:1). Boc-amino acids were obtained from Beckman Instruments, Inc. They were checked for homogeneity by thin layer chromatography and for optical purity by the Manning and Moore method.[33] Bpoc-amino acids were synthesized in this laboratory as cyclohexylamine or dicyclohexylamine salts and characterized as described recently.[34] Gly-Val, Gly-Gly, Gly-Gly-Gly, and Gly-Gly-Gly-Gly were obtained from Schwarz Bioresearch. Gly-Gly-Gly-Gly-Gly, Gly-Gly-Gly-Gly-Gly, and Gly-Gly-Val were purchased from Fox Chemical Co. Chloromethyl methyl ether (Aldrich Chemical Co.) was distilled in an efficient hood before use. *N,N'*-Dicyclohexylcarbodiimide (Schwarz), *N,N'*-carbonyldiimidazole (Aldrich), and ethyl and isobutyl chlorocarbonates (Eastman) were used without further purification. The resin support was a copolymer of styrene and 1% divinylbenzene (Bio-Rad), 200–400 mesh. It was chloromethylated to the extent of 1.2 mmol/g and esterified with Boc-Val by a procedure using triethylamine[35] or by the new cesium salt method.[36] No quaternary ammonium sites were formed with the latter procedure. Hydroxymethyl resin was prepared from chloromethyl resin *via* the acetoxymethyl derivative and was esterified by the carbonyldiimidazole procedure.[37] The general procedures for solid-phase synthesis were similar to those described earlier[14,37-39] but modified as indicated.

Synthesis of Leucyl-Alanyl-Glycyl-Valine by the Mixed Anhydride Method. Boc-valine-resin (1.2 g, 0.378 mmol Val) was placed in a water-jacketed reaction vessel and deprotected with 40 ml of 20% trifluoroacetic acid in methylene chloride for 30 min

at 25°. The resin was filtered, washed with CH_2Cl_2, neutralized with 10% Et_3N in CH_2Cl_2, and washed with CH_2Cl_2. Bpoc-glycine (313 mg) was dissolved in 10 ml of CH_2Cl_2 at 0° and mixed with 10 ml of 0.1 *M* Et_3N and 9 ml of 0.1 *M* EtOCOCl. The activation mixture was stirred for 30 min at 0°, filtered, diluted to 50 ml with CH_2Cl_2, and added to the valine-resin. The coupling mixture was shaken for 2 hr at 25°, filtered, and washed with CH_2Cl_2. The Bpoc group was removed by treatment with 1% TFA in CH_2Cl_2 for 20 min and the trifluoroacetate was neutralized with 10% Et_3N in CH_2Cl_2. Bpoc-alanine (327 mg) and Bpoc-leucine (468 mg) were coupled in a similar way to give the protected tetrapeptide Bpoc-Leu-Ala-Gly-Val-resin. In this synthesis the only solvent was CH_2Cl_2, but in other syntheses (see Table I) washes with 2-propanol were inserted between the CH_2Cl_2 washes following deprotection, neutralization, and coupling.

Part of the peptide resin (500 mg) was cleaved in 5 ml of redistilled HF and 0.5 ml of anisole at 0° for 1 hr.[40] After evaporation of the HF, the peptide was extracted from the resin with 10% aqueous acetic acid and then with glacial acetic acid. The combined filtrates were lyophilized; yield, 21 mg (40% from Boc-Val-resin). Amino acid analysis of the crude peptide resin showed Gly, 1.00; Ala, 0.95; Val, 1.05; Leu, 0.95. A second synthesis, in which ethyl chlorocarbonate was replaced by isobutyl chlorocarbonate, gave 39 mg (74%) of crude product.

Isolation of Leu-Ala-Gly-Val and Leu-Ala-Gly-Gly-Val. Part (5 mg) of the crude lyophilized product from the mixed anhydride synthesis of Leu-Ala-Gly-Val was dissolved in 1 ml of water and applied to the 0.9 × 60 cm column of the Beckman 120B amino acid analyzer which had been modified to enable the simultaneous analysis and isolation of peptide.[41] The column was packed with Beckman AA-15 cation exchange resin and was equilibrated with pH 3.49 citrate buffer (0.2 *N*) at 56°. The flow rate was 66 ml/hr. A divider pump was adjusted to remove 12 ml/hr and to allow the remaining 54 ml/hr to be collected in a fraction collector (1.5 min/tube). The diverted stream was mixed with buffer pumped at the rate of 54 ml/hr and then with ninhydrin at 33 ml/hr. The solution was passed through the reaction coil and colorimeter of the analyzer as usual and the results were plotted on the recorder (Figure 1). The delay between collection of a peak in the fraction collector and its detection on the recorder was 15 min. The main peak of Leu-Ala-Gly-Val (2.9 μmol) was in tubes 139–159 (peak at 234 min). A small amount of Ala-Gly-Val (0.076 μmol) was found in tubes 127–129 (peak at 201 min) and Leu-Ala-Gly-Gly-Val (0.084 μmol) was found in tubes 118–121 (peak at 189 min). Aliquots of the three fractions were hydrolyzed and the amino acid ratios were determined.

	Amino acid ratio			
Fraction	Gly	Ala	Val	Leu
118–121	1.97	1.00	1.04	0.85
127–129	0.90	1.00	1.01	0.05
139–159	1.03	1.00	1.02	0.99

Synthesis of Leucyl-Alanyl-Glycyl-Glycyl-Valine. Boc-Val-resin (2.35 g, 0.67 mmol) was deprotected with 20% TFA in CH_2Cl_2, neutralized with 10% Et_3N in CH_2Cl_2, and coupled for 2 hr with 4 equiv of Boc-Gly and 4 equiv of DCC in 50 ml of CH_2Cl_2. A sample of the Boc-Gly-Val-resin was removed for analysis and the remainder was extended by coupling in a similar way with Boc-Gly, Boc-Ala, and Boc-Leu. The resulting Boc-Leu-Ala-Gly-Gly-Val-resin was deprotected in TFA, hydrolyzed,[38] and analyzed: Gly, 1.98; Ala, 1.00; Val, 1.06; Leu, 0.92. A 500-mg sample of the peptide resin was cleaved in 5 ml of HF at 0° for 1 hr to yield 52 mg of peptide (94% from Boc-Val-resin). The pentapeptide (0.5 mg) was chromatographed on the 0.9 × 60 cm column of the amino acid analyzer in pH 3.49 buffer. The main peak emerged at 189 min and accounted for 96% of the product. This standard preparation of Leu-Ala-Gly-Gly-Val was cochromatographed on the same column with the corresponding pentapeptide isolated from the mixed anhydride synthesis. A single component emerged as a peak at 189 min.

To follow the progress of the pentapeptide synthesis and establish its structure, samples of peptide resin were removed at each step. Amino acid ratios were determined on acid hydrolysates, and the peptides were cleaved from the resin with HF and fractionated by ion exchange chromatography on the 0.9 × 60 cm column with pH 3.49 buffer.

	Elution	Amino acid ratios		
Peptide	time, min	Val	Gly	Ala
Gly-Val	268	1.00	1.00	
Gly-Gly-Val	218	1.10	2.00	
Ala-Gly-Gly-Val	167	1.02	2.00	0.97

Detection of Glycine Diketopiperazine after Mixed Anhydride Coupling with Val-Resin. Bpoc-Gly (0.045 mmol) was activated with triethylamine (0.045 mmol) and ethyl chlorocarbonate (0.040 mmol) for 24 hr at 0° in 1.3 ml of CH_2Cl_2 and shaken with 0.69 g (0.225 mmol) of valine resin in methylene chloride for 2 hr at room temperature. The filtrate was made 10% in trifluoroacetic acid and allowed to stand for 30 min, after which time the solvents were removed *in vacuo*. The resulting residue was kept overnight *in vacuo* in a desiccator containing calcium sulfate and phosphorous pentoxide. The residue was dissolved in hot DMF (0.5 ml) and allowed to cool to room temperature, whereupon some insoluble material was removed by centrifugation and samples from the supernatant were subjected to gas–liquid chromatography[18,19] in the absence and presence of glycine diketopiperazine. The column (6 ft × 3.5 mm of 3% EGSP-Z on Gas Chrom Q, 100–200 mesh) was maintained at 201° and the flow rates of the gases were kept at 44 (H_2), 60 (He), and 360 cm^3/min (air). A component was observed at 20 min, which cochromatographed with the authentic sample of glycine diketopiperazine dissolved in dimethylformamide. The filtrate was calculated to contain 0.0036 mmol of glycine diketopiperazine, which accounted for 18% of the activated Bpoc-glycine.

***N*-*tert*-Butyloxycarbonylglycyl-6-aminohexanoic Acid.** A modification of the Rothe and Kunitz[42] method for synthesis of 6-aminohexanoyl peptides was used in this preparation. A solution of Boc-Gly (1.40 g, 8.00 mmol) and triethylamine (1.16 ml, 8.40 mmol) in 20 ml of tetrahydrofuran was cooled to −15° in an ice–salt bath. Isobutyl chlorocarbonate (1.11 ml, 8.40 mmol) was added and the mixture was stirred for 8 min. A solution of 6-aminohexanoic acid, prepared by refluxing ε-caprolactam (0.900 g, 8.00 mmol) in 10 ml of 0.93 *N* aqueous sodium hydroxide, was added. The reaction mixture was stirred in the ice bath for 1 hr and at room temperature overnight. The clear, light brown solution was evaporated *in vacuo* to a residue, which was dissolved in water (20 ml), chilled in an ice bath, and acidified to pH 3.0 by addition of 3 *N* hydrochloric acid. The solution was saturated with sodium chloride and extracted with three 50-ml portions of ethyl acetate. The combined extracts were washed with four 50-ml portions of saturated aqueous sodium chloride, dried over magnesium sulfate, and freed of solvent to yield an oil (2.43 g). The oil contained the title compound, R_f 0.70 (CMA), contaminated with Boc-Gly, R_f 0.66 (CMA). The product was purified on a column (4.2 × 53 cm) of Sephadex LH-20 eluted with dimethylformamide. When the resulting oil, which was free of Boc-Gly by tlc, was allowed to stand under petroleum ether (bp 30–60°) in the cold for a week, a crystalline product (0.270 g) was isolated in low yield (12%), mp 87–89°.

Anal. Calcd for $C_{13}H_{24}N_2O_5$: C, 54.15; H, 8.39; N, 9.71. Found: C, 52.42; H, 8.38; N, 9.62.

A weighed portion of the above compound was treated with trifluoroacetic acid for 30 min at room temperature. The trifluoroacetic acid was removed *in vacuo* and the resulting glycyl-6-aminohexanoic acid trifluoroacetate was dissolved in an aqueous solution containing known quantities of ammonium chloride and 6-aminohexanoic acid. Glycyl-6-aminohexanoic acid cannot be resolved from 6-aminohexanoic acid on the short column (0.9 × 6 cm Beckman PA-35 cation exchange resin) of the amino acid analyzer under the usual conditions (sodium citrate, 0.35 *N*, pH 5.26, 65 ml/hr, 56°). A longer column (0.9 × 13 cm) of the same resin allowed good resolution of ammonium chloride (127 min), glycyl-6-aminohexanoic acid (149 min), and 6-aminohexanoic acid (175 min) when a modified buffer (sodium citrate, 0.20 *N*, pH 4.15, 1.5% benzyl alcohol, 2.0% 1-propanol) was used. The relative ninhydrin color values are 1.81:2.26:1.00 for ammonium chloride–glycyl-6-aminohexanoic acid–6-aminohexanoic acid.

Attempted Acylation of *N*-Benzyloxycarbonyl-6-aminohexanoyl Resin. The substituted resin was prepared by treating 6-(benzyloxycarbonylamino)hexanoic acid[42] with chloromethylated copoly(styrene–1% divinylbenzene) resin in the presence of triethylamine and dimethylformamide according to Marglin.[43] Amino acid analysis of the resin gave 0.108 mmol/g of 6-aminohexanoic acid.

A. Carbodiimide Method. A portion of the substituted resin (0.200 g, 0.0216 mmol) was placed in a 5-ml reaction vessel[19] and shaken (10 min) with 2 ml of methylene chloride containing Boc-Gly (0.306 g, 1.75 mmol). Dicyclohexylcarbodiimide (0.360 g, 1.75 mmol) in 2 ml of methylene chloride was added and shaking was continued for 12 hr. The resin was washed with methylene chloride (6 × 2 ml) and then shaken with a mixture of 2 ml of 32% HBr in acetic acid and 2 ml of TFA[44] for 100 min. The cleavage solution was filtered and the resin was washed with three 2-ml

portions of TFA, TFA–methylene chloride (1:1), and methylene chloride. The pooled filtrates were evaporated *in vacuo*. The resulting oil was suspended in methylene chloride and again evaporated *in vacuo*. This procedure was repeated several times to remove excess acid from the cleavage product. The residue was dissolved in 1 ml of glacial acetic acid. Addition of water (19 ml) produced a massive white precipitate of dicyclohexylurea. The suspension was shaken for several minutes and then filtered through a millipore disk prior to analysis with the amino acid analyzer. The presence of glycyl-6-aminohexanoic acid could not be detected (<0.1%); the presence of 20 μmol of 6-aminohexanoic acid indicated a cleavage efficiency of 93%.

B. Mixed Anhydride Method. A solution of 0.437 *M* Boc-glycine mixed anhydride was prepared by treating Boc-glycine (0.486 g, 2.78 mmol) and triethylamine (0.388 ml, 2.78 mmol) with isobutyl chlorocarbonate (0.346 ml, 2.62 mmol) in methylene chloride (6 ml) at −10° for 15 min. A portion (4 ml, 1.75 mmol) of this solution was shaken with 0.200 g of resin for 12 hr at 25° and worked up as described for the carbodiimide method. The presence of glycyl-6-aminohexanoic acid could not be detected (<0.1%); the presence of 156 μmol of 6-aminohexanoic acid indicated a cleavage efficiency of 78%.

Attempted Acylation of Boc-Gly-Gly-Resin. The substituted resin was prepared by treating Boc-Gly-Gly with chloromethylated resin (1% cross linked, 1.17 mmol Cl/g) according to Marglin.[43] Amino acid analysis of the resin indicated the presence of 0.136 mmol of glycylglycine/g. A portion of Boc-Gly-Gly-resin (0.200 g, 0.00272 mmol) was placed in a 5-ml reaction vessel and shaken (2 hr, 25°) with a solution (4 ml, 1.75 mmol) of 0.437 *M* Boc-glycine mixed anhydride, which was prepared as described above. The resin was washed with methylene chloride (6 × 2 ml) and then shaken for 15 min in 50% trifluoroacetic acid–methylene chloride (4 ml). The acid treatment was repeated and the resin was washed with methylene chloride (6 × 2 ml). It was treated with 10% triethylamine in methylene chloride (10 min), and washed with methylene chloride (6 × 2 ml). Cleavage of the resin with HBr was performed as described above. The presence of 20.8 μmol of glycylglycine indicated a cleavage efficiency of 77%. Triglycine, tetraglycine, pentaglycine, and hexaglycine could not be detected (<0.1% of Gly-Gly). When the sample was concentrated tenfold and applied to the analyzer column, the presence of a trace component running at the position of triglycine was detected (0.007 μmol, 0.03%). The presence of tetraglycine, pentaglycine, and hexaglycine could not be detected in the concentrated sample (<0.03%).

Beyerman, *et al.*,[45] have reported the formation of Gly-Gly-Gly-Gly-resin from Gly-Gly-resin in 1% yield when the latter was treated with 10% triethylamine in methylene chloride for 10 min. The dimerization reaction was thought to result from an interchain aminolysis. Our results contrast with this finding, since no tetraglycine (<0.03%) was detected after the treatment of deblocked Gly-Gly-resin with 10% triethylamine in methylene chloride for 10 min followed by cleavage with HBr.

Acknowledgments. We wish to thank Dr. B. W. Erickson for helpful discussions during the course of this work.

Registry No.—Leucyl-alanyl-glycyl-valine, 17195-26-5; Bpoc-glycine, 23650-19-3; ethyl chlorocarbonate, 541-41-3; leucyl-alanyl-glycyl-glycyl-valine, 49849-82-3; Boc-glycine, 4530-20-5; *N*-*tert*-butyloxycarbonylglycyl-6-aminohexanoic acid, 40203-83-6; isobutyl chlorocarbonate, 543-27-1; 6-aminohexanoic acid, 60-32-2; glycyl-glycyl-valine, 20274-89-9.

References and Notes

(1) Supported in part by Grant AM 01260 from the U. S. Public Health Service and by a grant from the Hoffmann-La Roche Foundation.
(2) The nomenclature and symbols follow the Tentative Rules of the IUPAC-IUB Commission on Biochemical Nomenclature, *J. Biol. Chem.*, **241**, 2491 (1966), **242**, 555 (1967), and **247**, 977 (1972). In addition, TFA = trifluoroacetic acid; Bpoc = 2-(4-biphenylyl)-2-propyloxycarbonyl = biphenylisopropyloxycarbonyl.
(3) T. Wieland and H. Bernard, *Justus Liebigs Ann. Chem.*, **572**, 190 (1951).
(4) R. A. Boissonnas, *Helv. Chim. Acta*, **34**, 874 (1951).
(5) J. R. Vaughan, Jr., *J. Amer. Chem. Soc.*, **73**, 3547 (1951).
(6) E. P. Semkin, N. D. Gafurova, and L. A. Shchukina, *Khim. Prir. Soedin.*, 3, 220 (1967).
(7) M. A. Tilak and C. S. Hollinden, *Tetrahedron Lett.*, 1297 (1968).
(8) C. L. Krumdieck and C. M. Baugh, *Biochemistry*, **8**, 1568 (1969).
(9) T. Wieland, C. Birr, and F. Flor, *Angew. Chem., Int. Ed. Engl.*, **10**, 336 (1971).
(10) F. Weygand, P. Huber, and K. Weiss, *Z. Naturforsch. B*, **22**, 1084 (1967).
(11) T. Wieland, C. Birr, R. Frodl, W. Lochinger, and G. Stahnke, *Justus Liebigs Ann. Chem.*, **757**, 136 (1972).
(12) H. Hagenmaier and H. Frank, *Hoppe-Seyler's Z. Physiol. Chem.*, **353**, 1973 (1972).
(13) N. F. Albertson, *Org. React.*, **12**, 157 (1962).
(14) R. B. Merrifield, *J. Amer. Chem. Soc.*, **85**, 2149 (1963); *Advan Enzymol.*, **32**, 221 (1969).
(15) R. B. Merrifield, in preparation.
(16) G. W. Anderson in "Progress in Peptide Research," Vol. 2, S. Lande, Ed., Gordon and Breach, New York, N. Y., 1972, pp 343–345.
(17) M. Zaoral and J. Rudinger, *Collect. Czech. Chem. Commun.*, **26**, 2316 (1961).
(18) A. B. Mauger, *J. Chromatogr.*, **37**, 315 (1968).
(19) B. F. Gisin and R. B. Merrifield, *J. Amer. Chem. Soc.*, **94**, 3102 (1972).
(20) D. F. DeTar, R. Silverstein, and F. F. Rogers, Jr., *J. Amer. Chem. Soc.*, **88**, 1024 (1966).
(21) M. Brenner in "Peptides, Proceedings of the Eighth European Peptide Symposium," H. C. Beyerman, A. Van De Linde, and W. Maassen Van Den Brink, Ed., Wiley, New York, N. Y., 1967, pp 1–7.
(22) A. R. Mitchell and R. W. Roeske, *J. Org. Chem.*, **35**, 1171 (1970).
(23) T. Wieland and H. Mohr, *Justus Liebigs Ann. Chem.*, **599**, 222 (1956).
(24) V. K. Antonov and M. M. Shemyakin, *Acta Chim. Acad. Sci. Hung.*, **44**, 93 (1965).
(25) P. Fankhauser, M. Schilling, and M. Brenner in "Peptides 1972, Proceedings of the Twelfth European Peptide Symposium," H. Hanson and H-D. Jakubke, Ed., Elsevier, New York, N. Y., 1973, pp 162–169.
(26) M. Bodanszky, R. J. Bath, A. Chang, M. L. Fink, K. W. Funk, S. M. Greenwald, and Y. S. Klausner in "Chemistry and Biology of Peptides, Proceedings of the Third American Peptide Symposium," J. Meienhofer, Ed., Ann Arbor Science Publishers, Ann Arbor, Mich., 1972, pp 203–207.
(27) K. D. Kopple and R. J. Renick, *J. Org. Chem.*, **23**, 1565 (1958).
(28) P. Schellenberg and J. Ullrich, *Chem. Ber.*, **92**, 1276 (1959).
(29) H. Determann in "Peptides, Proceedings of the Eighth European Peptide Symposium," H. C. Beyerman, A. Van De Linde, and W. Maassen Van Den Brink, Ed., Wiley, New York, N. Y., 1967, pp 73–78.
(30) H. Kotake and T. Saito, *Bull. Chem. Soc. Jap.*, **39**, 853 (1966).
(31) T. Wieland and B. Heinke, *Justus Liebigs Ann. Chem.*, **599**, 70 (1956).
(32) We are indebted to Dr. Joseph Rudinger for pointing out the need for this control.
(33) J. M. Manning and S. Moore, *J. Biol. Chem.*, **243**, 5591 (1968).
(34) R. S. Feinberg and R. B. Merrifield, *Tetrahedron*, **28**, 5865 (1972).
(35) G. R. Marshall and R. B. Merrifield, *Biochemistry*, **4**, 2394 (1965).
(36) B. F. Gisin, *Helv. Chim. Acta*, **56**, 1476 (1973).
(37) J. M. Stewart and J. D. Young, "Solid Phase Peptide Synthesis," W. H. Freeman, San Francisco, Calif., 1969.
(38) B. Gutte and R. B. Merrifield, *J. Biol. Chem.*, **246**, 1922 (1971).
(39) R. B. Merrifield, *J. Amer. Chem. Soc.*, **86**, 304 (1964).
(40) J. Lenard and A. B. Robinson, *J. Amer. Chem. Soc.*, **89**, 181 (1967).
(41) We are indebted to Drs. R. S. Hodges and B. W. Erickson for the design and construction of the modified apparatus.
(42) M. Rothe and F.-W. Kunitz, *Justus Liebigs Ann. Chem.*, **609**, 88 (1957).
(43) A. Marglin, *Tetrahedron Lett.*, 3145 (1971).
(44) B. F. Gisin, unpublished procedure. *Caution.* Pressure develops.
(45) H. C. Beyerman, E. W. B. de Leer, and W. van Vossen, *J. Chem. Soc., Chem. Commun.*, 929 (1972).

Synthesis of Antheridiol and Some Observations on the Chemistry of Butenolides

Trevor C. McMorris,*[1] Ramakrishnan Seshadri, and Thangavel Arunachalam

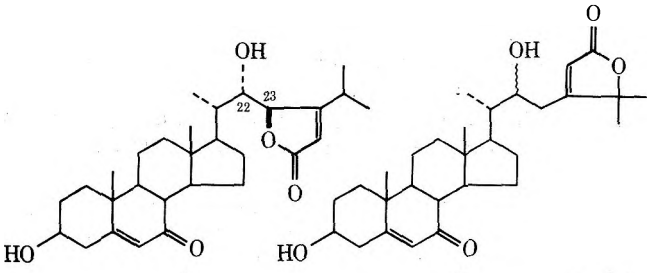
The New York Botanical Garden, Bronx, New York 10458

Received August 13, 1973

The fungal sex hormone, antheridiol, has been synthesized in an overall yield of ~20% by aldol condensation of 3β-acetoxy-22,23-bisnor-Δ⁵-cholenaldehyde and the carbanion of β-isopropylbut-2-enolide. This yielded the acetate of 7-deoxy-7-dihydroantheridiol (22*S*,23*R*) which was hydrolyzed and then subjected to photooxygenation and rearrangement to give antheridiol. The major product of the aldol condensation, the acetate of 7-deoxy-7-dihydroantheridiol (22*R*,23*S*), was converted to the desired isomer (22*S*,23*R*) by Jones oxidation followed by autoxidation and then borohydride reduction. The scope of the aldol condensation involving butenolides has been investigated.

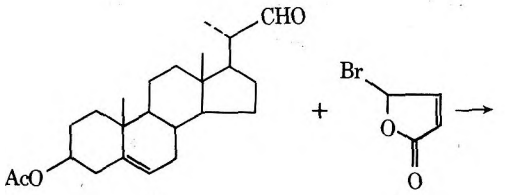
Antheridiol (**1**) is a hormonal substance which is secreted by female strains of the aquatic fungus, *Achlya*, and which acts on male strains causing the formation of antheridial hyphae, or male sex organs. Its isolation was reported in 1967[2] and the elucidation of its structure in 1968.[3] Shortly thereafter a synthesis was reported by workers at the Syntex Corp., Calif.[4] This paper gives details of work carried out at the New York Botanical Garden which has led to a practical synthesis of the hormone.[5]

Initially our objective was to synthesize the structure **1** without regard to the stereochemistry at C_{22} and C_{23}. The stereochemistry, which was unknown in 1968, has been determined mainly from synthetic experiments by the Syntex group. We planned to use a Reformatsky reaction to link a C_{22} aldehyde directly to a C_7 butenolide. A similar method had been used successfully to prepare the structure **2**, which at one time was suspected of being the structure of antheridiol itself.[6]

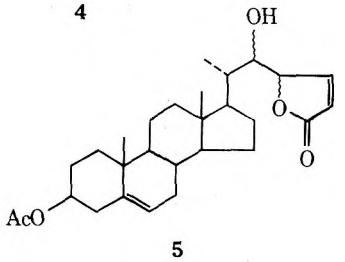


1 **2**

Model experiments were first carried out with 3β-acetoxy-22,23-bisnor-Δ⁵-cholenaldehyde (**3**) and the readily



3 **4**

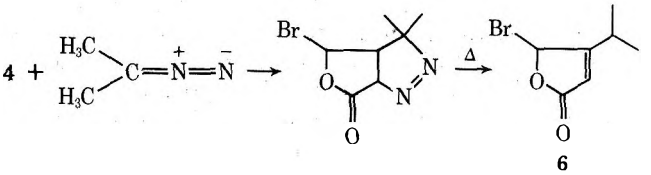


5

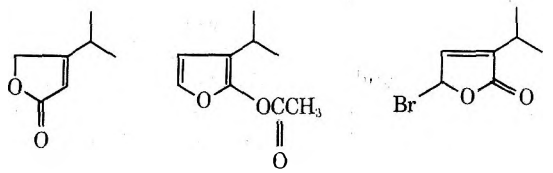
prepared bromobutenolide (**4**). When a solution of these compounds in benzene was heated with activated zinc dust, a very low yield (~5%) of a condensation product could be obtained. The crystalline product (mp 185–200°) had spectral properties consistent with structure **5**.

Thus the infrared spectrum had ν_{max} 3420 (hydroxyl), 1799, 1767, 1733 cm^{-1} (lactone and acetate), and the nmr spectrum showed, in particular, a doublet at δ 3.63 (J = 4.5 Hz) assigned to 22-H, a broad singlet at δ 5.9 assigned to 23-H and doublets at δ 6.2 (J = 6 Hz) and 7.2 (J = 6 Hz) assigned to 25-H and 24-H, respectively. The mass spectrum of **5** had the base peak at m/e 312 (M − CH_3COOH − 84) indicating ready cleavage at the C_{22}–C_{23} bond with transfer of one hydrogen to the lactone, similar to the case of antheridiol.

Encouraged by the success of the Reformatsky reaction, we proceeded to prepare γ-bromo-β-isopropylbut-2-enolide (**6**). This was accomplished by treating γ-bromobut-2-enolide (**4**) with an ethereal solution of 2-diazopropane.[7] An unstable pyrazoline was formed which on heating in xylene decomposed to give the desired compound in 35% yield. Two other methods of making **6** were tried but were unsuccessful. One method was allylic bromination of β-isopropylbut-2-enolide (**7**), which gave a monobromo derivative containing bromine exclusively in the side chain. The other involved acid-catalyzed pyrolysis of 2,5-diacetoxy-3-isopropyl-2,5-dihydrofuran. No 2-acetoxy-4-isopropylfuran could be isolated. Only isomer **8** was obtained and this, on bromination, gave γ-bromo-α-isopropylbut-2-enolide (**9**).[8]



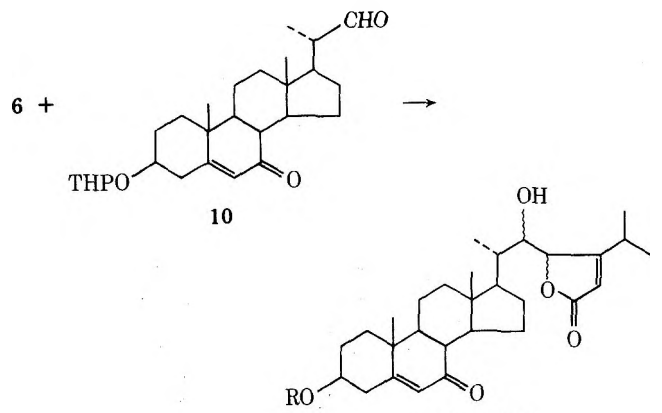
6



7 **8** **9**

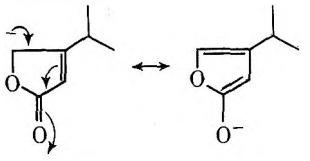
Reformatsky reaction of **6** and the aldehyde (**10**), which had been synthesized previously,[6] yielded a product which possessed approximately 1% of the biological activity of antheridiol. However, neither antheridiol nor any of its isomers could be isolated from acid hydrolysis of the product.

Other ways were therefore sought for condensing the butenolide with the aldehyde. An attempt was made to prepare the carbanion of **7**, which is the intermediate in the Reformatsky reaction above, by treatment of **7** with tritylllithium. We believed the carbanion should form



11, R = THP
12, R = H

readily because the electron-withdrawing effect of the lactone oxygen would enhance the acidity of the allylic hydrogen on the adjacent carbon atom. Resonance stabilization of the anion would also favor its formation.

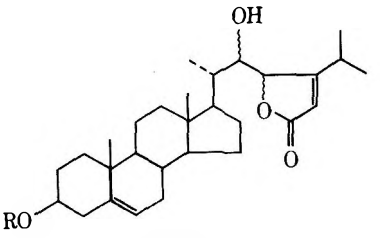


In the event, addition of a solution of **7** in tetrahydrofuran to a blood red solution of tritylllithium at −30° in an argon atmosphere resulted in rapid discharge of the color. The resulting pale yellow solution was immediately cooled to −70° and a solution of the aldehyde **10** in tetrahydrofuran added. The mixture was kept at −70° for 30 min; then the temperature was allowed to rise gradually to 0° during 30 min. The solution was then added to an excess of cold (0°) solution of dilute hydrochloric acid.

The product after chromatography (50% yield) exhibited biological activity about 10% that of antheridiol. The aldol reaction of **10** and **7** results in the creation of two new asymmetric centers (C_{22} and C_{23}), so that four stereoisomers were to be expected, provided no epimerization occurred at C_{20} in the reaction. In a similar condensation involving a C_{22} aldehyde, the Syntex workers found no evidence of epimerization at C_{20}.[4] Repeated chromatography resolved the product into two components, and these on gentle acid hydrolysis afforded mainly two isomers of antheridiol. Thus one of the hydrolyzed components had the same properties as those reported for the erythro isomer of antheridiol.[4] Recrystallization gave crystals with lower biological activity while the residue from the mother liquor had higher activity. However, no pure antheridiol could be obtained from this residue despite repeated recrystallization and chromatography. The erythro isomer and antheridiol (which also has the erythro configuration at C_{22},C_{23}) have the same R_f values in different solvent systems and could not be separated by chromatography. The other hydrolyzed component was later shown to be a mixture of threo isomers containing mainly the 22*R*,23*R* isomer.

Repetition of the aldol condensation of β-isopropylbut-2-enolide with 3β-acetoxy-22,23-bisnor-Δ⁵-cholenaldehyde yielded the product **13** (70%) and the corresponding diol **14** (5%).

The product was resolved by chromatography and fractional crystallization into the following components. The acetate of 7-deoxy-7-dihydroantheridiol (**13**, 22*S*,23*R*), mp 164–166°; the erythro isomer (**13**, 22*K*,23*S*), mp 219–223°; the threo isomer (**13**, 22*R*,23*R*), mp 202–208°; and the threo isomer (**13**, 22*S*,23*S*), mp 175–180°, 195–198°. These



13, R = Ac
14, R = H

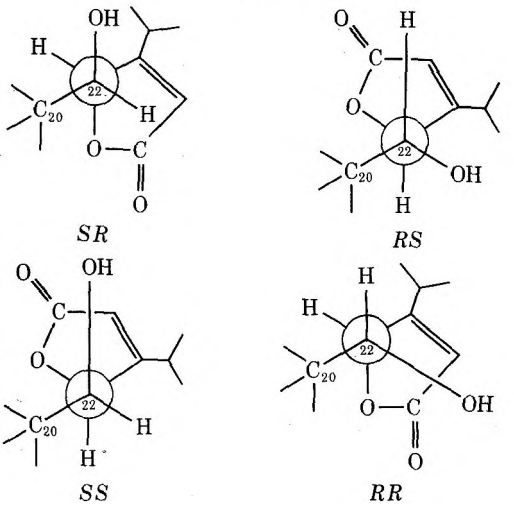
isomers were formed in a ratio of approximately 1:10:2:1 (see Experimental Section). The more polar fractions from the chromatography were a mixture of isomers of 7-deoxy-7-dihydroantheridiol, containing mainly the erythro isomer (**14**, 22*R*,23*S*). The acetates were cleanly resolved on thin layer chromatography (tlc) using ethyl acetate–petroleum ether or benzene–ether as solvents. The evidence for the assignment of stereochemistry to the four $C_{22}C_{23}$ stereoisomers is presented later. The mass spectra of the acetates were very similar. All showed the highest peak at *m/e* 438, which corresponds to loss of acetic acid from the molecular ion (M^+ 498). The most intense peaks occurred at *m/e* 312 and 126 and result from a McLafferty rearrangement involving cleavage of the C_{22}–C_{23} bond and transfer of a hydrogen to the lactone fragment. This cleavage is characteristic of the antheridiol side chain.

The infrared (ir) spectra of the acetates taken in KBr showed several differences from each other. The butenolide and acetate carbonyl absorptions were partly merged, the former appearing as a shoulder in the acetate peak in the *SR* and *SS* isomers, but as a distinct peak in the *RR* isomer. The carbonyl region in the *RS* isomer was more complex, four distinct peaks being observed: 1818 (w), 1767 (s), 1739 (m), and 1715 cm^{-1} (s).

The nmr spectra of the acetates afforded the best means of distinguishing the isomers. In particular, the coupling constant between 22-H and 23-H in the erythro isomers was 8.5–9.0 Hz, while for the threo isomers 23-H appeared as a broad singlet indicating only weak coupling with 22-H. These coupling constants are expected for erythro and threo isomers from a consideration of nonbonded interactions.[9]

It is clear from the Newman projections (Scheme I) shown that the conformer which contributes most (to the mixture of the three staggered forms) will in both cases, *SR* and *RS*, have a dihedral angle of 180° between the protons, leading to a large coupling constant. In the threo isomers the conformer which contributes most will have a dihedral angle of 60°, leading to a small coupling con-

Scheme I



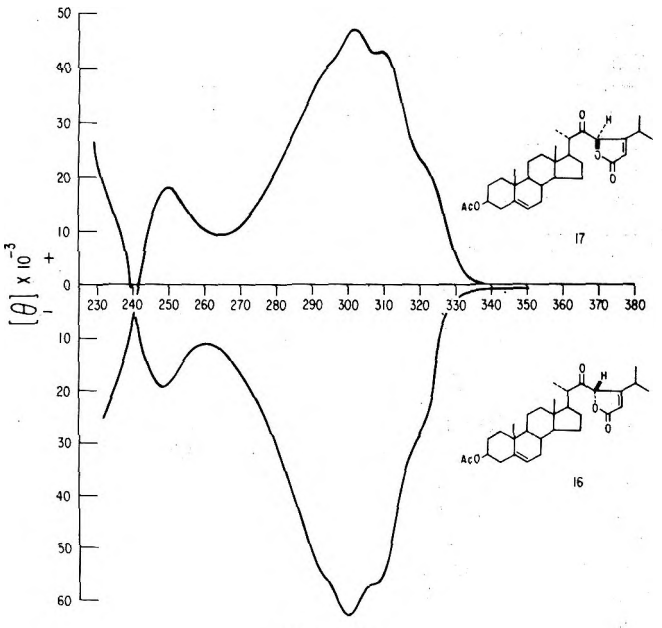


Figure 1.

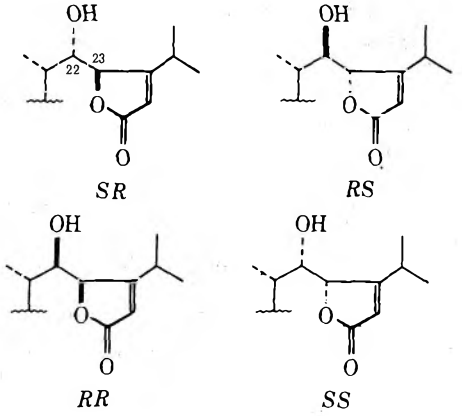
stant, as is actually observed. In fact, the large difference in the observed values for the erythro and threo isomers suggests that each isomer exists mainly in a single conformation.

The coupling constant between 22-H and 20-H appeared to be small for all except the 22*S*,23*S* isomer in which a value of 5 Hz was observed. The C_{26} and C_{27} methyl groups appeared as a pair of doublets (J = 7 Hz) in all four compounds.

The condensation of the aldehyde **3** and the butenolide **7** is quite stereoselective, one major product, the 22*R*,23*S* isomer, being formed. The stereoselectivity at C_{22} is similar to that obtained in other reported condensations involving steroidal C_{22} aldehydes. For example, an attempted synthesis of 23-deoxyantheridiol yielded only the C_{22} epimer (22*S*).[10] The configuration at C_{22} is correctly predicted by Cram's rule as noted by Barton and coworkers.[11]

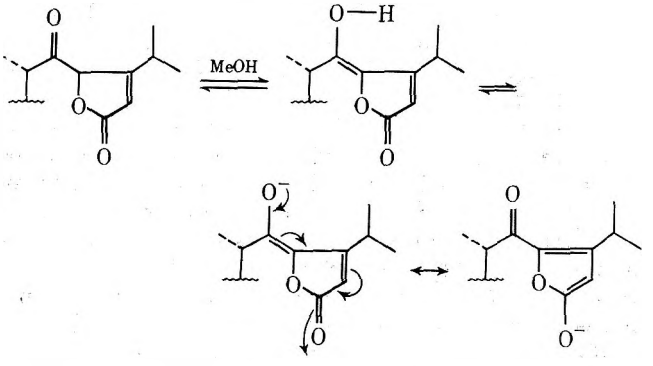
Since the yield of the isomer possessing the same side-chain stereochemistry as antheridiol (*i.e.*, 22*S*,23*R*) was low, attempts were made to change the stereochemistry at C_{22} and C_{23} in the other isomers by an oxidation–reduction sequence. Thus Jones oxidation of **13** (22*R*,23*S*) gave an almost quantitative yield of the 23*S* ketone **16** (mp 154–158°, crude product). Similarly Jones oxidation of **13** (22*R*,23*R*) gave the 23*R* ketone **17**, mp 156–160°. The nmr spectra of the two ketones differ particularly in the chemical shifts of the C_{18} and C_{21} methyl groups and of the 23-H proton. The circular dichroism curves are most distinctive, the curve for the 23*S* ketone being practically the mirror image of that of the 23*R* isomer (Figure 1). The very high values observed for the molar ellipticity indicate that rotation about the C_{22}–C_{23} bond is quite restricted and one rotamer predominates in the case of the 23*R* isomer and one in the case of the 23*S* isomer.[12] The situation is similar to that in the 22-hydroxy compounds (**13**) discussed above.

If the octant rule is applied to models of the two ketones arranged so that steric interactions are at a minimum, the butenolide ring will fall in a positive octant for the 23*R* isomer and in a negative octant for the 23*S* isomer. Therefore, the CD curves predict the same configurations for the isomers as is found from the following independent evidence. The acetate **13**, mp 164–166°, which can be converted directly to antheridiol, and the acetate **13**, mp 219–223°, are erythro isomers from nmr evidence described above. In addition, the latter compound can be hydrolyzed to give a diol which has the same properties as those reported for the erythro isomer of 7-deoxy-7-dihydroantheridiol.[4] The configuration at C_{22} and C_{23} in antheridiol has been definitely assigned as 22*S*,23*R*.[13] The erythro isomer **13**, mp 219–223°, which must therefore be 22*R*,23*S*, will give on oxidation a ketone possessing the *S* configuration at C_{23}. Since oxidation of **13**, mp 202–208°, yields a different ketone from that obtained from **13**, mp 219–223°, the former ketone has the 23*R* configuration and the parent compound is a threo isomer (22*R*,23*R*). The fourth isomer **13**, mp 175–180°, 195–198°, has the threo configuration (22*S*,23*S*) also.

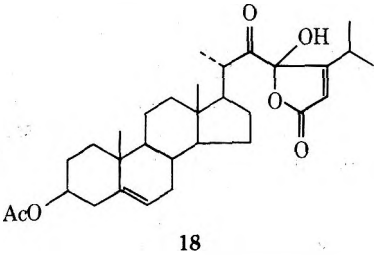


The CD curves of the ketones **16** and **17** were measured in chloroform or dioxane in which the compounds are stable. In solution in methanol the ketones both showed uv maxima at 321 and 363 nm. Addition of a drop of alkali caused a sharp increase (over tenfold) in the intensity of the 363-nm maximum and disappearance of the 321-nm maximum, indicating that the former was produced by the enolate anion shown (Scheme II). In agreement, acidification resulted in immediate disappearance of the 363-nm peak and reappearance of the 321-nm peak.

Scheme II



When the ketone **16** or **17** was run on tlc with ethyl acetate–petroleum ether, a single spot with an R_f greater than that of the parent alcohol **13** was observed. However, if the developing solvent was chloroform–methanol, at least three spots resulted. Examination of these spots



18

showed that the ketone was undergoing autoxidation and the main product was identified as the 23-hydroxy ketone **18**.

The yield of **18** could be increased to about 80% by stirring a solution of **16** or **17** in tetrahydrofuran–methanol (3:1) with silica gel overnight. A by-product of the reaction was 3β-acetoxy-22,23-bisnor-Δ^5-cholenic acid, formed by oxidative cleavage of the C_{22}–C_{23} bond in **16** or **17**.

The ketones undergo autoxidation very readily because the enolate anion can form in the presence of methanol which acts as a base. The reaction of an enolate anion with molecular oxygen is well known, and a mechanism can be written which explains the formation of the two products.[14,15]

The formation of the hydroxy ketone **18** was important because this compound could be cleanly reduced with sodium borohydride to one having the hydroxy butenolide side chain of antheridiol. Treatment of **16** itself with sodium borohydride in ethanol gave a yellow solution of the enolate anion and no hydroxy butenolide could be isolated. It is interesting to note that butenolides containing hydrogen on the γ carbon such as antheridiol and β-isopropylbut-2-enolide are attacked by borohydride with reduction of the double bond. When the γ position is fully substituted as in β,γ,γ-trimethylbut-2-enolide, no reduction of the double bond occurs. Presumably the presence of a γ hydrogen will result in the formation of a carbanion in the presence of base. Rearrangement gives a carbonyl (*via* an enol) which is reduced by the borohydride.

Different conditions for the reduction of **18** were tried. The most satisfactory was reaction of excess sodium borohydride with a solution of **18** in tetrahydrofuran–ethanol (3:1) at 10° for 20 hr. A nearly quantitative yield of **13** was obtained which contained approximately 20% of the 22*S*,23*R* isomer. This isomer could be separated and the remaining material put through the oxidation–reduction sequence again in order to produce more of the desired isomer. In this way the yield of **13** with the side-chain stereochemistry of antheridiol could be increased considerably.

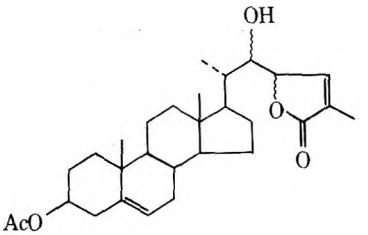
An attempt was also made to invert the configuration at C_{22} in the isomer **13** (22*R*,23*R*). Treatment of the latter with methanesulfonyl chloride gave the 22-mesylate as well as much elimination product. However when the mesylate was heated with tetrabutylammonium formate, only elimination occurred.[16] This result is not surprising since the C_{22} position is hindered and elimination will be favored over substitution. Elimination also produces an extended conjugated system, another reason in its favor.

In order to complete the synthesis of antheridiol, the acetate **13** (22*S*,23*R*) was hydrolyzed to the diol. Conditions had to be carefully chosen since the hydroxy butenolide structure was sensitive to base and to hydrochloric acid in methanol. However dilute sulfuric acid in dioxane gave a very high yield of the diol.

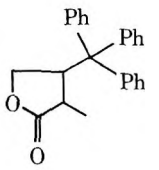
The final step in the synthesis was the introduction of the 7-ketone. The most convenient method was that first employed by the Syntex group.[4] Photooxygenation of the diol **14** in the presence of a sensitizer, hematoporphyrin, gave a high yield of the 5α-hydroperoxide. The hydroperoxide from the 22*R*,23*S* isomer was quite unstable and was easily converted to the 7-ketone in about 60% yield by treatment with cupric chloride in pyridine for 24 hr. The hydroperoxide from the 22*S*,23*R* isomer was obtained crystalline. It was more stable and longer treatment and more cupric chloride were required in order to obtain a 50% conversion to the corresponding 7-ketone (antheridiol).

Another method of introducing the 7-ketone involved conversion of the diol **14** to the bistetrahydropyranyl ether. The latter was then oxidized with Collins reagent to give the 7-ketone.[17] Careful acid hydrolysis removed the tetrahydropyranyl protecting groups though some elimination of the 3β-hydroxyl could not be prevented. The yield in this method was about 35%. The synthetic antheridiol had the same properties, including biological activity, as the natural hormone. The method of synthesis described here affords pure antheridiol in an overall yield of approximately 20% from the readily accessible 3β-acetoxy-22,23-bisnor-Δ^5-cholenaldehyde (**3**). The results of biological tests of antheridiol and certain synthetic intermediates in *Achlya* and other systems will be reported elsewhere.

The scope of the aldol condensation of butenolides such as **7** with aldehydes has been investigated further. When excess of α-methylbut-2-enolide[18] was added to tritylithium and the resulting pale yellow solution treated with the aldehyde **3**, a low yield (~30%) of condensation product was obtained. Spectral and analytical properties support the structure **19**. As in the case of **13** a mixture of four stereoisomers is formed, the main component being probably the 22*R*,23*S* isomer. The major product (50%) from the condensation was a crystalline compound whose spectral properties indicated the structure **20**. Thus the mass spectrum showed the molecular ion at *m/e* 342 and base peak at *m/e* 243 ($C_{19}H_{15}^+$), the latter due to the triphenylmethyl ion. The lactone **20** results from nucleophilic attack of trityl carbanion on the β carbon of the butenolide.[19] The hindered tertiary carbanion appears to be involved rather than one of the ring carbons as observed in the reaction of tritylithium and benzophenone.[20] In the latter case the nmr spectrum of the adduct showed a signal at δ 5.53. Triphenylmethane itself shows a methine-H singlet at δ 5.52. No signal occurs in this region for the adduct **20**.

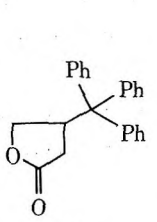


19

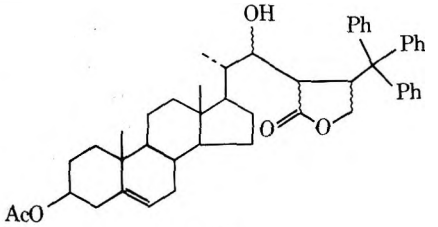


20

The reaction which gives **20** competes well with abstraction of a γ hydrogen from the butenolide. When aldol condensation was attempted with but-2-enolide,[18] no product analogous to **13** could be isolated. As expected, lactone **21**, the Michael adduct of triphenylmethane and but-2-enolide, was obtained, though in low yield (10%). The major product (70%) was a steroid which is assigned the structure **22**.



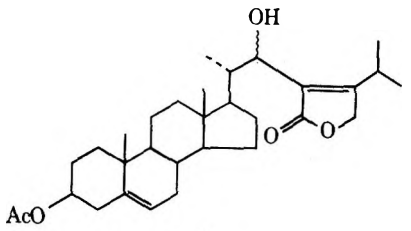
21



22

Because but-2-enolide has no methyl group which can hinder the approach of the trityl anion and also contribute an inductive effect, adduct formation proceeds almost exclusively in this case. The intermediate α anion then reacts with the steroid aldehyde to give **22**. The condensation product **22** has been partially resolved.

Another interesting possibility in condensations involving butenolides was observed in snythesis of **13**. A byproduct (5%) which was present in chromatographic fractions containing **13** (22*R*,23*S*) had properties consistent with the structure **23**. In particular, the nmr spectrum



23

showed a singlet at δ 4.74 for two protons α to oxygen in the butenolide ring. β-Isopropylbut-2-enolide (**7**) shows a corresponding signal at δ 4.80 (d, J = 2 Hz). Oxidation of **23** with Jones reagent gave the 22-ketone, λ_{max} 232 nm (ϵ 11,900). The uv spectrum was not affected by alkali (*cf.* **16**). The formation of **23** involves addition of the α carbanion of **7** to the aldehyde **3** followed by rearrangement of the intermediate anion to give the α,β-unsaturated butenolide.[21]

Experimental Section[22]

Reformatsky Reaction of 3β-Acetoxy-22,23-bisnor-Δ^5-cholenaldehyde (3) and γ-Bromobut-2-enolide (4). The method was the same as that used for the preparation of **2** described in an earlier paper.[6] Chromatography of the crude product with ethyl acetate–petroleum ether gave a fraction which crystallized on adding methanol. The crystals of **5** obtained in a yield of 5% from the aldehyde appeared homogeneous by tlc: mp 185–200°; ir 3420, 1799, 1767, 1733 cm^{-1}; nmr δ 0.71 (18 H), 1.03 (19 H), 1.04 (d, J = 6 Hz, 21 H), 2.03 (acetate), 3.63 (d, J = 4.5 Hz, 22 H), 5.37 (m, 6 H), 5.9 (m, 23 H), 6.22 (d, J = 6 Hz, 25 H), 7.21 (d, J = 6 Hz, 24 H); mass spectrum m/e 396 (M − 60), 312 (M − 60 − 84), 84 ($C_4H_4O_2^+$).

β-Isopropylbut-2-enolide (7). To a three-necked flask in an ice-salt bath were added acetic anhydride (2 l.), potassium acetate (260 g), and 3-methylbut-1-ene (50 g). The mixture was stirred and powdered $KMnO_4$ (340 g) added gradually during 3 hr.[23] Care was taken to maintain the temperature of the mixture below 5°. The stirring was continued for a further 5 hr at ~5° and then cold ethyl acetate (2 l.) was added, followed by an ice-cold solution of sodium bisulfite (450 g) in water (3.5 l.). The organic layer was separated and the aqueous solution neutralized with sodium bicarbonate and extracted with ethyl acetate. The combined ethyl acetate extract was washed with saturated $NaHCO_3$ solution, water, then dried (Na_2SO_4), and distilled to give 1-acetoxy-3-methylbutan-2-one (37 g): bp 90° (2 mm); ir (neat) 1730 cm^{-1}; nmr δ 1.12 (d, J = 7 Hz, isopropyl CH_3), 2.13 (acetate), 2.72 (m, methine H), 4.74 (s, methylene H). An alternative method for making this compound involved reaction of isopropylmagnesium bromide with glycolonitrile and acetylation with acetic anhydride–pyridine of the product, 1-hydroxy-3-methylbutan-2-one.[24] The ketoacetate (37 g) and ethyl bromoacetate (45 g) in dry benzene (180 ml) were added gradually to activated zinc dust,[6] and the mixture was gently warmed. When the reaction became vigorous, the heating was stopped and the remaining solution added at such a rate as to maintain the reflux. The mixture was refluxed for a further 2 hr. It was cooled, diluted with benzene, and acidified with dilute H_2SO_4. The benzene layer was separated, washed with water, and dried (Na_2SO_4); the solvent was removed, leaving an oil which was chromatographed, then distilled under reduced pressure to give **7**, (10 g): bp 90° (1.75 mm); ir 1775, 1740, 1626 cm^{-1}; nmr δ 1.22 (d, J = 7 Hz, isopropyl CH_3), 2.75 (m, methine H), 4.84 (d, J = 2 Hz, methylene H), 5.83 (q, vinyl H).

The butenolide **7** (126 mg) in carbon tetrachloride (3 ml) was heated with *N*-bromosuccinimide (178 mg) under illumination from a 100-W lamp. The reaction was complete within 30 min. The mixture was cooled and filtered, and the solvent was removed from the filtrate leaving a yellow oil. This gave a single spot on tlc and the nmr indicated that bromine was present exclusively in the allylic position on the side chain: nmr (CCl_4) δ 2.05 (s, CH_3), 5.02 (d, J = 2 Hz, methylene H), 4.95 (t, J = 2 Hz, vinyl H).

Pyrolysis of 2,5-Diacetoxy-3-isopropyl-2,5-dihydrofuran. 4-Isopropyl-2-furoic acid was prepared according to the method of Elming.[25] Decarboxylation by the method of Piers and Brown[26] gave better yields of β-isopropylfuran than those reported by Elming.[25] Treatment of the furan with lead tetraacetate afforded the diacetoxy dihydro derivative.[27] The latter compound (250 mg) and a crystal of toluenesulfonic acid[28] were heated at 100° for 10 min in a sublimation tube under reduced pressure (2 mm). The liquid darkened rapidly and a distillate was formed which collected in a trap cooled with Dry Ice–acetone. The distillate (~100 mg) was a mixture of acetic acid and 2-acetoxy-3-isopropylfuran (**8**). The nmr spectrum (CCl_4) of **8** had δ 1.14 (d, J = 7 Hz, isopropyl CH_3), 2.25 (acetate), 2.65 (quintet, J = 7 Hz, methine H), 6.23 (d, J = 2 Hz, 4 H), 6.98 (d, J = 2 Hz, 5 H). The structure was confirmed by adding a solution of bromine in carbon tetrachloride to one of the furan in carbon tetrachloride (cooled to −10°) until the bromine color just persisted. Excess of bromine was avoided by adding a little more of the furan.[27] The nmr spectrum (CCl_4) of the product, γ-bromo-α-isopropylbut-2-enolide (**9**) had δ 1.24 (d, J = 7 Hz, isopropyl CH_3), 2.75 (quintet, J = 7 Hz, methine H), 6.83 (t, J = 1 Hz, γ H), 7.1 (t, J = 1 Hz, β H).

γ-Bromo-β-isopropylbut-2-enolide (6). 2-Acetoxyfuran was converted to γ-bromobut-2-enolide[27] which was purified by distillation followed by chromatography with ethyl acetate–petroleum ether: nmr (CCl_4) δ 6.2 (pair of d, J = 5 and 1 Hz, α H), 7.0 (t, J = 1 Hz, γ H), 7.70 (pair of d, J = 5 and 1 Hz, β H). The bromobutenolide (2.2 g) was treated with an excess of an ethereal solution (0°) of 2-diazopropane[7] (100 ml) prepared from acetonehydrazone (5 g). Reaction was rapid as indicated by immediate discharge of the red color. Toward the end of the addition the color persisted and some oily material separated. The reaction mixture was kept at 0° overnight; then benzene (100 ml) was added and the mixture concentrated to one-half the volume. (If all the solvent was removed the pyrazoline rapidly polymerized to a black tar and gas was evolved.) Xylene (100 ml) was next added and the mixture again concentrated to one-half the volume. Finally more xylene (50 ml) was added and the mixture refluxed for 3 hr. Most of the xylene was distilled off [40–50° (1.0 mm)] and the residue chromatographed with ethyl acetate–petroleum ether (1:9) to give **6** in 35% yield: ir 1799, 1767 sh, 1637 cm^{-1}; nmr (CCl_4) δ 1.18, 1.33 (pair of d, J = 7 Hz, isopropyl CH_3), 2.89 (m, methine H), 5.83 (d, J = 1 Hz, α-H), 6.75 (s, γ-H); mass spectrum m/e 204 (M^+), 206.

Anal. Calcd for $C_7H_9O_2Br$: C, 40.98; H, 4.39; O, 15.61; Br, 39.02. Found: C, 40.74; H, 4.53; O, 15.79: Br, 39.26.

Reformatsky Reaction of 3β-Tetrahydropyranyloxy-22,23-bisnor-Δ^5-7-ketocholenaldehyde (10) and γ-Bromo-β-isopropylbut-2-enolide (6). The aldehyde (800 mg) and the bromobutenolide (400 mg) were dissolved in dry benzene (20 ml), and the solution was refluxed with activated zinc dust (200 mg) as described earlier.[6] The crude product had about 1% of the biological activity of antheridiol. A portion of the product was treated with dilute HCl in methanol (0.08 ml of 6 *N* HCl in 100 ml of methanol) to remove the tetrahydropyranyl group and then chromatographed with ethyl acetate–petroleum ether. However, no crystalline antheridiol or any of its isomers could be isolated.

Condensation of Aldehyde 10 with β-Isopropylbut-2-enolide (7). Butyllithium (0.6 g, 90% in hydrocarbon, obtained from Ventron Corp., Beverly, Mass.) was weighed into a three-necked flask previously flushed out with argon. Extreme care was taken to avoid contact with air during the weighing. (The butyllithium was stored in a desiccator with an argon atmosphere.) Triphenylmethane (2.86 g) in tetrahydrofuran (10 ml) freshly distilled from lithium aluminum hydride, was added dropwise during 10 min to the butyllithium in the flask (argon atmosphere), cooled to *ca* −30° in an acetone bath containing enough Dry Ice to maintain the temperature. A deep red solution formed immediately. The solution was stirred (magnetic stirrer) at −30° for 30 min, then allowed to come gradually to room temperature, and stirred for a further 30 min. It was then cooled to −30° and a solution of **7** (1.0 g) in tetrahydrofuran (15 ml) was added dropwise with stirring. Towards the end of the addition, which required only a few minutes, the red color was discharged. The pale yellow solution was quickly cooled to *ca.* −72° and the aldehyde **10** (1.25 g) in tetrahydrofuran (25 ml) added gradually. The reaction mixture was stirred at −72° for a further 30 min and then allowed to come to room temperature during 30 min. It was added to an excess of dilute HCl (0°) with vigorous stirring. A semisolid precipitate was

obtained, so the mixture was extracted with ether and the extract washed (H_2O) and dried (Na_2SO_4). The ether was distilled off and the residue chromatographed with ethyl acetate–petroleum ether. Early fractions gave triphenylmethane. The crystalline condensation product **11** (0.7 g) possessed about 10% of the biological activity of antheridiol. It was resolved by further chromatography into two main components. One component (0.4 g) was recrystallized from methanol: mp 221–223°; ir 1767, 1660, 1626 cm^{-1}; nmr δ 0.70 (18 H), 1.04 (d, J = 7 Hz, 21 H), 1.20 (19 H), 1.19, 1.23 (pair of d, J = 7 Hz, 26 and 27 H), 3.64 (d, J = 9 Hz, 22 H), 4.90 (d, J = 9 Hz, 23 H), 5.68 (s, 6 H), 5.75 (t, J = 1 Hz, 28 H).

Anal. Calcd for $C_{34}H_{50}O_6 \cdot 0.25CH_3OH$: C, 73.07; H, 9.13; O, 17.77. Found: C, 73.06; H, 9.55; O, 17.25.

This component was hydrolyzed by treatment with dilute HCl in methanol (0.08 ml of 6*N* HCl in 100 ml of methanol at 0° for 30 min). The crystalline product obtained in high yield was also ~10% as active as antheridiol. It gave a single spot on tlc which had the same R_f as antheridiol in all solvent systems studied, *e.g.* in $CHCl_3$–MeOH (15:1), R_f 0.43. Recrystallization from methanol gave long needles, mp 260–265° dec. The spectral properties were identical with those of the erythro isomer of antheridiol (see later). The biological activity of the crystals was less than that of the starting material, while that of the residue from the mother liquor was higher. However, despite further crystallization and chromatography of the residue, no pure antheridiol could be isolated. The major component of the condensation product is thus the erythro isomer (22*R*,23*S*). The other main component (0.17 g) on hydrolysis gave crystals of the threo isomer (22*R*,23*R*) of antheridiol (see later).

Condensation of 3β-Acetoxy-22,23-bisnor-Δ⁵-cholenaldehyde (3) with β-Isopropylbut-2-enolide (7) *n*-Butyllithium (1.68 g) was treated with excess of triphenylmethane (8.6 g) in tetrahydrofuran (35 ml) to form trityllithium as described above. The red solution was treated with an excess of **7** (2.71 g in 20 ml of tetrahydrofuran) and the resulting carbanion allowed to react with the aldehyde **3** (6.32 g in 40 ml of tetrahydrofuran). The gummy product (17.6 g) was chromatographed with ethyl acetate–petroleum ether, 100-ml fractions being collected. Early fractions contained triphenylmethane. Unreacted aldehyde (~1.2 g) was eluted in fractions 13–17. It was followed by a product (~0.5 g) formed from elimination of the 22-OH in **13**. Unreacted butenolide, **7**, was eluted in the first fractions, 21–23, containing **13** (22*S*,23*R*). Fractions 23–25 contained almost pure **13** (22*S*,23*R*) (0.47 g) which was recrystallized from ethyl acetate–petroleum ether: mp 164–166°; ir 1760 sh, 1733, 1637 cm^{-1}; nmr δ 0.70 (18 H), 1.02 (19 H), 1.17, 1.22 (pair of d, J = 6.5 Hz, 26 and 27 H), 2.03 (acetate), 3.61 (d, J = 9 Hz, 22 H), 4.94 (d, J = 9 Hz, 23 H), 5.4 (m, 6 H), 5.78 (t, J = 1 Hz, 28 H); mass spectrum m/e 438, 420, 312, 126; CD max $[\theta]_{218nm}$ +37,350° (dioxane).

Anal. Calcd for $C_{31}H_{46}O_5$: C, 74.66; H, 9.30. Found C, 74.24; H, 9.45.

Fractions 26 and 27 contained the isomer **23** which was obtained pure after recrystallization from methanol (50 mg): mp 169–171°, on further heating it solidified then melted again at 180–181°; ir 1740, 1667 cm^{-1}; nmr δ 0.70 (18 H), 1.02 (19 H), 1.12 (d, J = 6.5 Hz, 26 and 27 H), 2.02 (acetate), 3.49 (d, J = 3 Hz, 22 H), 4.74 (s, 28 H), 5.37 (m, 6 H); mass spectrum m/e 438, 420.

Anal. Found: C, 74.75; H, 9.52.

Fractions 26–39 were mainly **13** (22*R*,23*S*) (4.29 g) which on recrystallization from methanol or ethyl acetate–petroleum ether gave pure compound: mp 219–223°; ir 1818 (w), 1767 (s), 1739 (w), 1715 cm^{-1} (s); nmr δ 0.72 (18 H), 1.03 (19 H), 1.05 (d, J = 6.5 Hz, 21 H), 1.18, 1.23 (pair of d, J = 7 Hz, 26 and 27 H), 2.03 (acetate), 3.6 (d, J = 8.5 Hz, 22 H), 4.91 (d, J = 8.5 Hz, 23 H), 5.4 (m, 6 H), 5.77 (t, J = 1 Hz, 28 H); mass spectrum m/e 438, 420, 312, 126; CD max $[\theta]_{218nm}$ −49,800° (dioxane).

Anal. Found: C, 74.54; H, 9.33.

Fractions 45–55 were mainly **13** (22*R*,23*R*) (0.9 g) which on recrystallization from ethyl acetate–petroleum ether gave pure compound: mp 204–208°; ir 1760, 1733, 1637 cm^{-1}; nmr δ 0.73 (18 H), 1.03 (19 H), 1.13 (d, J = 6 Hz, 21 H), 1.17, 1.25 (pair of d, J = 7 Hz, 26 and 27 H), 2.03 (acetate), 3.9 (broad s, 22 H), 4.9 (broad s, 23 H), 5.4 (m, 6 H), 5.82 (t, J = 1 Hz, 28 H); mass spectrum m/e 438, 420, 312, 126.

Anal. Found: C, 74.63; H, 9.03.

Fractions 56–58 contained mainly **13** (22*S*,23*S*) (~0.5 g) but with a small amount of the isomer **13** (22*R*,23*R*). Preparative tlc followed by recrystallization gave pure **13** (22*S*,23*S*): mp 175–180°, 195–198°; ir 1736, 1637 cm^{-1}; nmr δ 0.75 (18 H), 1.03 (19 H), 1.13 (d, J = 7 Hz, 21 H), 1.18, 1.26 (pair of d, J = 7 Hz, 26 and 27 H), 2.02 (acetate), 3.89 (d, J = 4.5 Hz, 22 H), 5.07 (broad s, 23 H), 5.4 (m, 6 H), 5.82 (t, J = 1 Hz, 28 H); mass spectrum m/e 438, 420, 312, 126.

Anal. Found: C, 74.35; H, 9.31.

Later fractions from the chromatography contained a mixture of isomers of 7-deoxy-7-dihydroantheridiol (**14**) (~0.2 g), but these could be separated only by preparative tlc with multiple development.

Hydrolysis of the 3-Acetate of 7-Deoxy-7-dihydroantheridiol (13). A solution of the acetate **13** (22*S*,23*R*) (45 mg) in dioxane (20 ml) was refluxed with 5% H_2SO_4 (5 ml) for 1 hr. Most of the solvent was removed under reduced pressure and cold water added, giving a crystalline precipitate of the diol **14** (38 mg). On crystallization from methanol it had mp 234–238°: ir 1740 cm^{-1}; nmr δ 0.70 (18 H), 1.02 (19 H), 1.17, 1.22 (pair of d, J = 6.5 Hz, 26 and 27 H), 3.61 (d, J = 9 Hz, 22 H), 4.94 (d, J = 9 Hz, 23 H), 5.4 (m, 6 H), 5.78 (t, J = 1 Hz, 28 H).

Anal. Calcd for $C_{29}H_{44}O_4 \cdot 0.25CH_3OH$: C, 75.65, H, 9.70. Found: C, 75.98; H, 9.95.

The erythro isomer **14** (22*R*,23*S*) was obtained in the same way: mp 209–211°; ir 7167 sh, 1745 cm^{-1}; nmr δ 0.72 (18 H), 1.02 (19 H), 1.04 (d, J = 7 Hz, 21 H), 1.18, 1.23 (pair of d, J = 7 Hz, 26 and 27 H), 3.61 (d, J = 8.5 Hz, 22 H), 4.93 (d, J = 8.5 Hz, 23 H), 5.38 (m, 6 H), 5.79 (t, J = 1 Hz, 28 H); mass spectrum m/e 456 (M^+), 438, 420, 405, 330, 312, 297, 284, 271, 255, 213.

Anal. Calcd for $C_{29}H_{44}O_4 \cdot 0.25CH_3OH$: C, 75.65; H, 9.70. Found: C, 75.56, H, 9.98.

Similar hydrolysis of the threo isomer **13** (22*R*,23*R*) gave the corresponding diol: mp 192–196° (methanol); ir 1748 cm^{-1}; nmr δ 0.73 (18 H), 1.03 (19 H), 1.13 (d, J = 6 Hz, 21 H), 1.17, 1.25 (pair of d, J = 7 Hz, 26 and 27 H), 3.94 (broad s, 22 H), 4.91 (broad s, 23 H), 5.38 (m, 6 H), 5.83 (t, J = 1 Hz, 28 H).

Anal. Calcd for $C_{29}H_{44}O_4 \cdot CH_3OH$: C, 73.73; H, 9.90. Found: C, 73.84; H, 9.69.

Hydrolysis of the threo isomer **13** (22*S*,23*S*) gave the corresponding diol: mp 248–252° (ethyl acetate); ir 1745 cm^{-1}; nmr ($CDCl_3$–CD_3OD, 3:1) δ 0.78 (18 H), 1.03 (19 H), 1.13 (d, J = 7 Hz, 21 H), 1.21, 1.28 (pair of d, J = 7 Hz, 26 and 27 H), 4.05 (broad peak, 22 H), 5.11 (broad s, 23 H), 5.33 (m, 6 H), 5.82 (t, J = 1 Hz, 28 H).

Anal. Calcd for $C_{29}H_{44}O_4$: C, 76.27; H, 9.71. Found: C, 75.76; H, 9.61.

Antheridiol (1). A solution of 130 mg of the diol **14** (22*S*,23*R*) and 13 mg of hematoporphyrin in 18 ml of pyridine contained in a Pyrex tube 2 cm × 15 cm was irradiated for 24 hr with two 15-W fluorescent lamps placed close to the tube while oxygen was passed through the solution.[4] The dark brown solution was diluted with ether (100 ml), stirred with activated charcoal, and then filtered through Celite. Removal of solvent from the filtrate gave the crystalline hydroperoxide which from tlc appeared nearly pure. It was dissolved in 10 ml of pyridine and, after adding 6 mg of $CuCl_2 \cdot 2H_2O$, was allowed to stand at room temperature for 3 days. (Shorter times resulted in lower yields of antheridiol.) The pyridine was removed *in vacuo* and the residue chromatographed (preparative tlc, two silica gel plates, $CHCl_3$–MeOH, 15:1) to give 66 mg of pure antheridiol: mp 244–248° dec (methanol): ir 1740, 1672, 1626 cm^{-1}; nmr ($CDCl_3$–CD_3OD, 3:1) δ 0.72 (18 H), 1.23 (19 H), 1.17, 1.23 (pair of d, J = 7 Hz, 26 and 27 H), 3.6 (broad d, J = 8 Hz, 22 H), 4.98 (broad d, J = 8 Hz, 23 H), 5.70 (s, 6 H), 5.79 (broad s, 28 H).

The erythro isomer of antheridiol was prepared similarly from the diol **14** (22*R*,23*S*) (100 mg). The intermediate hydroperoxide was less stable and could not be isolated crystalline. Treatment with $CuCl_2 \cdot 2H_2O$ (3 mg) for 24 hr gave the 7-ketone (62 mg): mp 260–263° (methanol); ir 1759, 1650, 1631 cm^{-1}; nmr ($CDCl_3$–CD_3OD, 3:1) δ 0.74 (18 H), 1.06 (d, J = 6.5 Hz, 21 H), 1.23 (19 H), 3.6 (d, J = 8.5 Hz, 22 H), 4.96 (d, J = 8.5 Hz, 23 H), 5.7 (s, 6 H), 5.78 (t, J = 1 Hz, 28 H).

Anal. Calcd for $C_{29}H_{42}O_5 \cdot 0.25CH_3OH$: C, 73.37; H, 9.06. Found: C, 73.41; H, 9.13.

The threo isomer (22*R*,23*R*) of antheridiol (29 mg) was prepared from the diol **14** (22*R*,23*R*) (42 mg): mp 209–213° (ethyl acetate–petroleum ether); ir 1761, 1742, 1678, 1637 cm^{-1}.

Anal. Calcd for $C_{29}H_{42}O_5$: C, 74.01; H, 9.00. Found: C, 74.32; H, 9.11.

The threo isomer (22*S*,23*S*) (18 mg) was prepared from the diol **14** (22*S*,23*S*) (25 mg): mp 260–263°; ir 1742, 1672, 1637 cm^{-1}; nmr ($CDCl_3$–CD_3OD, 4:1) δ 0.78 (18 H), 1.23 (19 H), 1.21, 1.26 (pair of d, J = 7 Hz, 26 and 27 H), 5.13 (broad s, 23 H), 5.71 (s, 6 H), 5.85 (t, J = 1 Hz, 28 H).

An alternative route to antheridiol and its isomers was as fol-

lows: 50 mg of the diol **14** (22*R*,23*S*) was converted to the bis-tetrahydropyranyl ether with dihydropyran and a trace of *p*-toluenesulfonic acid. The ether was dissolved in methylene chloride (3 ml), and a slurry of 400 mg of Collins reagent[17] in methylene chloride (2 ml) was then added. Tarry material formed quickly. The mixture was stirred for 18 hr, more Collins reagent (150 mg) added, and the stirring continued for 7 hr. The mixture was filtered through a column of silica gel and the column eluted with ethyl acetate. Removal of solvent from the combined filtrate gave 35 mg of the 7-ketone. It was treated with dilute HCl in methanol (0.08 ml of 6*N* HCl in 100 ml of MeOH) for 1 hr at room temperature. Ethyl acetate was added; then most of the solvent was removed in a stream of N_2 and the residue chromatographed with chloroform–methanol (15:1) to give 17 mg of the erythro isomer of antheridiol. About 6 mg of the $\Delta^{3,5}$-dien-7-one was also obtained. This resulted from elimination of the 3β substituent.

Oxidation of the Acetate of 7-Deoxy-7-dihydroantheridiol (13). Jones reagent[29] (4 ml) was gradually added to a stirred solution of **13** (22*R*,23*S*) (1 g) in 150 ml of acetone cooled to 0°. The mixture was kept at 0° for 1 hr; then methanol was added to destroy any excess reagent. Most of the solvent was removed *in vacuo*, and cold water added to precipitate the crystalline ketone **16** (0.98 g): mp 154–158°; uv max (MeOH) 212 nm (ϵ 7000), 225 sh (6000), 321 (1900), 363 (650). The intensity of the 321- and 363-nm maxima depended on the concentration of the solution, being more intense at lower concentrations; uv (MeOH/drop of dilute NaOH solution) 363 nm (ϵ 30,000); uv (MeOH/dilute HCl) 212 nm (ϵ 6200), 225 sh (5900), 321 (2100); ir 1802, 1770, 1733, 1724 cm^{-1}; nmr δ 0.67 (18 H), 1.02 (19 H), 1.18 (d, J = 7 Hz, 21 H), 1.21, 1.23 (pair of d, J = 7 Hz, 26 and 27 H), 2.03 (acetate), 5.33 (d, J = 2 Hz, 23 H; the signal partly overlapped that at 5.4 due to 6 H), 5.92 (t, J = 1 Hz, 28 H); mass spectrum m/e 436 (M − 60), 421, 371, 328, 279; CD max $[\theta]_{301}$ −61,400°.

Oxidation of 55 mg of **13** (22*R*,23*R*) in the same way with Jones reagent gave 52 mg of the ketone **17**: mp 156–160°; uv same as that of **16**; ir 1802, 1770, 1733, 1724 sh cm^{-1}; nmr δ 0.73 (18 H), 0.98 (d, J = 7 Hz, 21 H), 1.03 (19 H), 1.21, 1.23 (pair of d, J = 7 Hz, 26 and 27 H), 2.03 (acetate), 5.23 (d, J = 2 Hz, 23 H), 5.4 (m, 6 H), 5.88 (t, J = 1 Hz, 28 H); CD max $[\theta]_{302}$ +46,000°.

Autoxidation of Ketone 16. A solution of 500 mg of **16** in 150 ml of tetrahydrofuran–methanol (2:1) was stirred with 20 g of silica gel-G for 24 hr. The uv spectrum (NaOH–MeOH) then showed that no starting material remained. The solution was filtered and the solvent removed leaving a white solid which was crystallized from ethyl acetate–petroleum ether to give 200 mg of the 23-hydroxy ketone (**18**). Chromatography of the residue from the mother liquor gave 175 mg more of **18**: mp 214–217°; ir 3340, 1779, 1730, 1709 cm^{-1}; nmr δ 0.67 (18 H), 1.01 (19 H), 2.02 (acetate), 5.4 (m, 6 H), 6.11 (d, J = 1.5 Hz, 28 H); mass spectrum m/e 452 (M − 60). 408, 283 (base peak).

Anal. Calcd for $C_{31}H_{44}O_6$: C, 72.63; H, 8.65; O, 18.72. Found: C, 72.44; H, 8.59; O, 18.94.

Later fractions from the chromatography gave 70 mg of a pure compound which was identified as 3β-acetoxy-22,23-bisnor-Δ^5-cholenic acid by comparison with an authentic sample. Several experiments were performed in which the concentration of **16**, the nature of the solvent, and the amount of silica were varied. The conditions described above gave the best yield of **18**.

Sodium Borohydride Reduction of 18. Sodium borohydride (15 mg) was added to a solution of 30 mg of **18** in 3 ml of tetrahydrofuran–ethanol (3:1) and the mixture allowed to stand at 10° for 20 hr. The solvent was removed in a stream of N_2 and water followed by a few drops of dilute HCl was added to the residue. The white insoluble solid was filtered, washed (H_2O), dried, and chromatographed to give 6 mg of **13** (22*S*,23*R*), 16 mg of **13** (22*R*,23*S*), and 5 mg of a mixture of the threo isomers of **13**. The reduction was repeated with different solvents, *e.g.*, tetrahydrofuran–methanol, 2-propanol, and dioxane–water, but the proportion of the desired isomer **13** (22*S*,23*R*) was not as good as that obtained above. When ethanol alone was used as solvent, an almost quantitative yield of diols **14** was obtained.

Condensation of Aldehyde 3 with α-Methylbut-2-enolide.[18] The butenolide (1.33 g) and the aldehyde (4.0 g) were condensed in the same way as described earlier for the preparation of **13**. The crude product (8.3 g) on chromatography with ethyl acetate–petroleum ether gave first the adduct **20** (2.3 g): mp 221–222° (ethyl acetate), uv max (EtOH) 199 nm (ϵ 72,400), 245 (687), 258 (730), 265 (653), 271 (425); ir 1767, 1600, 1496 cm^{-1}; nmr δ 1.40 (d, J = 7.5 Hz, methyl), 2.58 (d of q, J = 8 Hz, J = 2.5 Hz, methine H), 3.8–4.8 (m, methine H + 2H α to oxygen), 7.25 (s, 15 aromatic H); mass spectrum m/e 342 (M$^+$), 243 ($C_{19}H_{15}^+$, base peak), 165 ($C_{13}H_9^+$).

Anal. Calcd for $C_{24}H_{22}O_2$: C, 84.18; H, 6.48. Found: C, 84.34; H, 6.46.

Later fractions from the chromatography contained an isomeric mixture of **19** (1.85 g). The main component was obtained pure by recrystallization from ethyl acetate–petroleum ether: mp 220–224°; ir 1767 sh, 1733 cm^{-1}; nmr δ 0.72 (18 H), 1.03 (19 H), 1.95 (t, J = 1.5 Hz, 27 H), 2.03 (acetate), 3.53 (d, J = 7 Hz, 22 H), 4.93 (m, 23 H) 5.4 (m, 6 H), 7.03 (t, J = 1.5 Hz, 24 H); mass spectrum m/e 410 (M − 60), 312 (M − 98 − 60).

Anal. Calcd for $C_{29}H_{42}O_5$: C, 74.01; H, 9.00. Found: C, 73.79; H, 9.11.

The other components of the isomeric mixture were present in smaller amount and were well resolved on tlc, but were not examined in detail.

Condensation of Aldehyde 3 with But-2-enolide.[18] But-2-enolide (1.83 g) and the aldehyde (6.1 g) were condensed as described above and the crude product (15.4 g) was recrystallized from ethyl acetate (5.1 g). A portion of this material (200 mg) was resolved into two components by preparative tlc with $CHCl_3$–MeOH (100:3). One component, **22** (81 mg), had mp 168–174°, 236–238° (MeOH): ir 1780 sh, 1761, 1739, 1603, 1497, 1475, 754, 745, 705 cm^{-1}; nmr δ 0.65 (18 H), 0.83 (d, J = 7 Hz, 21 H), 1.00 (19 H), 2.03 (acetate), 2.78 (d, J = 10 Hz, 23 H), 5.4 (m, 6 H), 7.30 (s, 15 aromatic H); mass spectrum m/e 312, 243, 165.

Anal. Calcd for $C_{29}H_{42}O_5$: C, 74.01; H, 9.00. Found: C, 73.79; C, 79.74; H, 8.21.

The other component, **22** (95 mg), had mp 241–244° (EtOAc): ir 1773 sh, 1745, 1600, 1498, 1475, 762, 748, 705 cm^{-1}; nmr δ 0.73 (18 H), 0.73 (d, J = 6 Hz, 21 H), 1.02 (19 H), 2.02 (acetate), 2.68 (d, J = 5.5 Hz, 23 H), 5.40 (m, 6 H), 7.26 (s, 15 aromatic H); mass spectrum m/e 397 (M − 243 − 60), 312 (M − 243 − 60 − 85), 243 ($C_{19}H_{15}^+$ base peak), 165 ($C_{13}H_9^+$).

Anal. Calcd for $C_{47}H_{56}O_5$: C, 80.53; H, 8.05. Found: C, 80.26; H, 7.90.

The material (10.3 g) in the mother liquor from recrystallization of **22** was chromatographed with ethyl acetate–petroleum ether to give the adduct **21** (0.84 g) contaminated with steroidal material **22**). It was freed from the contaminant by acid hydrolysis which deacetylated the steroid and then chromatography with $CHCl_3$–MeOH (50:1): mp 207–209° (ethyl acetate–petroleum ether); uv max 199 nm (ϵ 31,100), 253 (561), 259 (630), 264 (596), 270 (365); ir 1764, 1600 cm^{-1}; nmr δ 2.47–2.83 (m, methylene H), 4.2–4.6 (m, methine H + methylene H α to oxygen); 7.26 (s, 15 aromatic H); mass spectrum m/e 328 (M$^+$), 243 ($C_{19}H_{15}^+$, base peak), 165 ($C_{13}H_9^+$).

Anal. Calcd for $C_{23}H_{20}O_2$: C, 84.12; H, 6.14. Found: C, 84.09; H, 6.10.

Acknowledgments. We are grateful to Dr. Alma Barksdale for the biological assays, to Helen McMorris for technical assistance, to Dr. T. T. Herskovits, Fordham University, for the CD spectra, and to the National Institutes of Health (Grant No. GM 12150) for support of this work.

Registry No.—(22*S*,23*R*)-**1**, 22263-79-2; (22*R*,23*S*)-**1**, 22233-25-6; (22*R*,23*R*)-**1**, 49686-14-8; (22*S*,23*S*)-**1**, 49686-15-9; **3**, 10211-88-8; **4**, 40125-53-9; **5**, 686-18-2; **6**, 35457-50-2; **7**, 10547-89-4; **8**, 49686-20-6; **9**, 49686-21-7; **10**, 49686-22-8; (22*R*,23*S*)-**11**, 49686-23-9; (22*S*,23*R*)-**13**, 37926-51-5; (22*R*,23*S*)-**13**, 37926-52-6; (22*R*,23*R*)-**13**, 37926-53-7; (22*S*,23*S*)-**13**, 37926-54-8; (22*S*,23*R*)-**14**, 35878-68-3; (22*R*,23*S*)-**14**, 49686-29-5; (22*R*,23*R*)-**14**, 35878-70-7; (22*S*,23*S*)-**14**, 35878-69-4; **16**, 37926-55-9; **17**, 38672-73-0; **18**, 37926-57-1; **19**, 49686-34-2; **20**, 49686-35-3; **21**, 49686-36-4; **22**, 49686-37-5; **23**, 49686-38-6; 3-methyl-1-butene, 563-451; 1-acetoxy-3-methylbutan-2-one, 36960-07-3; brominated butenolide, 49686-40-0; 2,5-diacetoxy-3-isopropyl-2,5-dihydrofuran, 49686-41-1; 2-diazopropane, 2684-60-8.

References and Notes

(1) To whom correspondence should be addressed at the University of California, San Diego, La Jolla, Calif. 92037.
(2) T. C. McMorris and A. W. Barksdale, *Nature (London)*, **215**, 320 (1967).
(3) G. P. Arsenault, K. Biemann, A. W. Barksdale, and T. C. McMorris, *J. Amer. Chem. Soc.*, **90**, 5635 (1968).
(4) J. A. Edwards, J. S. Mills, J. Sundeen, and J. H. Fried, *J. Amer. Chem. Soc.*, **91**, 1248 (1969).
(5) Preliminary communications: T. C. McMorris and R. Seshadri, *Chem. Commun.*, 1646 (1971), T. C. McMorris, T. Arunachalam, and R. Seshadri, *Tetrahedron Lett.*, 2673 (1972).

(6) T. C. McMorris, J. Org. Chem., 35, 458 (1970).
(7) A. C. Day, P. Raymond, R. M. Southam, and M. C. Whiting, J. Chem. Soc., 467 (1966). See also M. Franck-Neumann, Angew. Chem., 80, 42 (1968).
(8) N. Elming and N. Clauson-Kaas, Acta Chem. Scand., 6, 565 (1952).
(9) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, Oxford, 1969, p 291.
(10) D. M. Green, J. A. Edwards, A. W. Barksdale, and T. C. McMorris, Tetrahedron, 27, 1199 (1971).
(11) D. H. R. Barton, J. P. Poyser, and P. G. Sammes, J. Chem. Soc. Perkin Trans. 1, 53 (1972).
(12) P. Crabbé, "Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry," Holden-Day, San Francisco, Calif., 1965, p 143.
(13) J. A. Edwards, J. Sundeen, W. Salmond, T. Iwadare, and J. H. Fried, Tetrahedron Lett., 791 (1972).
(14) E. J. Bailey, D. H. R. Barton, J. Elks, and J. F. Templeton, J. Chem. Soc., 1578 (1962).
(15) W. von E. Doering and R. M. Haines, J. Amer. Chem. Soc., 76, 482 (1954).
(16) E. J. Corey and S. Terashima, J. Org. Chem., 37, 3043 (1972).
(17) W. G. Dauben, M. Lorber, and D. S. Fullerton, J. Org. Chem., 34, 3587 (1969).
(18) M. Franck-Neumann and C. Berger, Bull. Soc. Chim. Fr., 4067 (1968).
(19) R. A. Lee and W. Reusch, Tetrahedron Lett., 969 (1973).
(20) P. Tomboulian and K. Stehower, J. Org. Chem., 33, 1509 (1968).
(21) Cf. E. Pfeffer, L. S. Silbert, and E. Kinsel, Tetrahedron Lett., 1163 (1973).
(22) Melting points were taken on a Kofler hot stage and are uncorrected. Infrared spectra were determined in KBr disks with a Perkin-Elmer Model 21 spectrophotometer and ultraviolet spectra were determined in ethanol with a Carey Model 17 spectrophotometer. Nuclear magnetic resonance spectra were recorded on a Varian A-60A spectrometer using tetramethylsilane as internal reference and $CDCl_3$ as solvent unless otherwise indicated. Mass spectra were determined by Morgan-Schaffer Corp., Montreal, on a Hitachi Perkin-Elmer RMU-6D spectrometer equipped with a direct inlet system at 190° and ionizing potential of 70 eV. Microanalyses were carried out by Dr. F. Pascher, Bonn. Silica gel (0.05–0.2 mm) was used for column chromatography and plates, 20 × 20 cm^2, coated with a 2-mm layer of silica gel containing fluorescent indicator, UV 254 (Brinkman Instruments, Inc., New York, N. Y.), were used for preparative thin layer chromatography. Petroleum ether had a boiling range of 60–80°.
(23) K. B. Sharpless, R. F. Lauer, Oljan Repič, A. Y. Teranishi, and D. R. Williams, J. Amer. Chem. Soc., 93, 3303 (1971).
(24) E. Pfeil and H. Barth, Justus Liebigs Ann. Chem., 593, 81 (1955).
(25) N. Elming, Acta Chem. Scand., 6, 605 (1952).
(26) E. Piers and R. K. Brown, Can. J. Chem., 40, 559 (1962).
(27) N. Elming, Acta Chem. Scand., 6, 578 (1952).
(28) M. P. Cava, C. L. Wilson, and C. J. Williams, Jr., J. Amer. Chem. Soc., 78, 2303 (1956).
(29) A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, J. Chem. Soc., 2555 (1953).

Alkaloids of *Cephalotaxus harringtonia* var. *drupacea*. 11-Hydroxycephalotaxine and Drupacine[1a]

Richard G. Powell,* Richard V. Madrigal, Cecil R. Smith, Jr., and Kenneth L. Mikolajczak

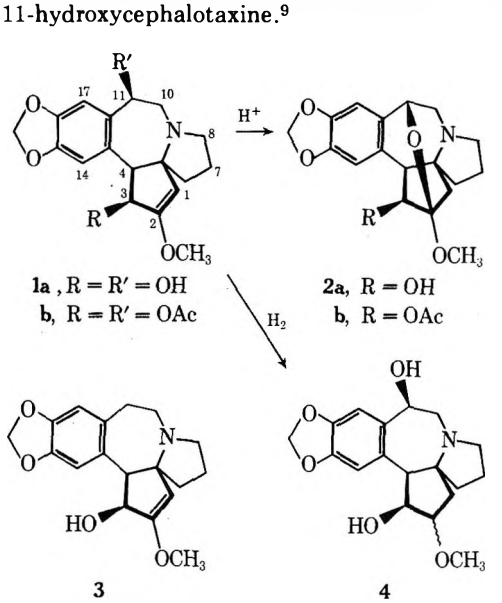
Northern Regional Research Laboratory,[1b] Peoria, Illinois 61604

Received July 27, 1973

Two isomeric alkaloids, 11-hydroxycephalotaxine and drupacine, have been isolated from *Cephalotaxus harringtonia* var. *drupacea* (Sieb. + Zucc.) Koidzumi. Evidence is presented to show that these alkaloids are represented by structures **1a** and **2a**, respectively. Close proximity of the two hydroxyl functions of **1a** leads to some unusual reaction products. Nearly quantitative conversion of **1a** to ketal **2a** occurs under mild acidic conditions. Treatment of **1a** with tosyl chloride in pyridine affords cyclic ether **5**, and oxidation of **1a** under modified Oppenauer conditions results in formation of hemiketal **7**. The diacetate of **1a** is epimerized under extraordinarily mild conditions.

Initial investigations of the alkaloids of *Cephalotaxus drupacea* were carried out by Paudler, *et al.*,[2] and by McKay.[3] Although earlier listed as a member of the family Taxaceae,[4] the genus *Cephalotaxus* has now been assigned to a separate family, the Cephalotaxaceae, and the plant formerly referred to as *C. drupacea* is now considered to be *C. harringtonia* var. *drupacea*.[5] Two different structural types of *Cephalotaxus* alkaloids have been noted; the first group is based on the cephalotaxine ring system (**3**), and the second group embodies the homoerythrina ring system.[6,7] Several natural cephalotaxine esters have recently gained attention as potential tumor inhibitors.[8] This paper gives details of the structural determinations of two oxygenated cephalotaxine derivatives first noted in a seed extract of *C. harringtonia* var. *drupacea* and describes some unusual reactions of hydroxycephalotaxine. Portions of this work were described in a preliminary communication.[9]

Alkaloids **1a**, **2a**, and **3** were isolated by preparative tlc of an alkaloid concentrate from *C. harringtonia* var. *drupacea* twigs. The first of these (**1a**, $C_{18}H_{21}NO_5$, $[\alpha]^{26}D$ −139°) had a broad hydroxyl band in its ir spectrum (3500 cm^{-1}) indicative of strong intramolecular hydrogen bonding. An nmr spectrum of **1a** contained signals (Table I) that allowed assignment of the cephalotaxine (**3**) ring system to **1a** and, in addition, exhibited a signal at δ 4.78 which was assigned to a proton on a carbon bearing both hydroxyl and aryl groups (C_{11}). Preparation of a di-*O*-acetyl derivative (**1b**, $C_{22}H_{25}NO_7$) demonstrated that **1a** contained two hydroxyl groups. Signals attributed to protons on the two hydroxyl-bearing carbons (C_3 and C_{11}) were shifted markedly downfield, as expected, upon acetylation of **1a**. These observations led to the conclusion that **1a** was an 11-hydroxycephalotaxine.[9]



The second alkaloid was isomeric with **1a** (**2a**, $C_{18}H_{21}NO_5$, $[\alpha]^{26}D$ −137°), and its ir spectrum demonstrated the presence of at least one hydroxyl group (3600

Table I
Nmr Data for Hydroxycephalotaxine (1) and Some Reaction Products[a]

Protons and assignments	Alkaloid 1a	1b	2a	2b	4	5	7	9
H-1	4.68 s	4.74 s	1.49 d	1.55 d		4.56 s	4.60 s	5.33 s
H-1′			2.65 d	2.70 d				
$J_{1,1'}$			14.0	14.0				
H-3	4.48 d	5.71 d	3.99 d	4.78 d	4.12 t	4.05 d		5.72 d
H-4	3.48 d	3.57 d	3.45 d	3.75 d	3.16 m	3.17 d	3.24 s	3.58 d
$J_{3,4}$	8.0	8.0	9.0	9.0		5.0		8.0
H-10	3.21 m	3.26 m	3.05 m	3.07 m	3.16 m	2.77 d	2.79 m	4.25 q[b]
H-11	4.78 t	6.17 t	4.87 q	4.90 q	4.71 q	4.74 t	4.76 m	6.34 q
H-14	6.62 s	6.58 s	6.65 s	6.51 s	6.56 s	6.64 s	6.67 s	6.59 s
H-17	6.88 s	6.70 s	6.65 s	6.63 s	6.81 s	6.67 s	6.73 s	6.69 s
$-OCH_3$	3.71 s	3.68 s	3.47 s	3.45 s	3.39 s	3.68 s	3.72 s	3.80 s
$-OCH_2O$	5.91 s	5.90 s	5.82 s	5.87 m	5.87 s	5.89 s	5.89 s	5.97 s
$-OC(=O)CH_3$		1.85 s		1.66 s				1.88 s
		2.06 s						2.09 s

[a] Measured in $CDCl_3$ with a Varian HA-100 spectrometer. Chemical shifts (δ) are expressed in ppm from tetramethylsilane and coupling constants (J) are expressed in Hz. [b] This signal is due to only one of the H-10 protons.

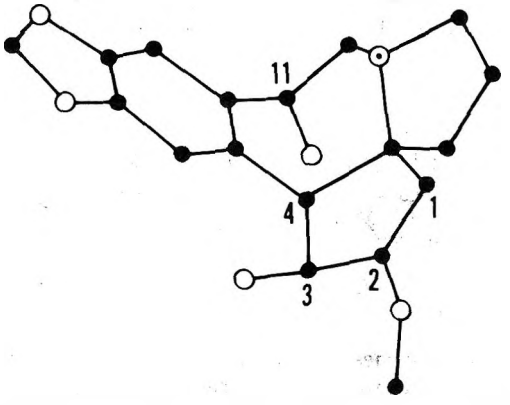


Figure 1. Stereoformula of 11-hydroxycephalotaxine (**1a**): O, carbon; ⊙, nitrogen; O, oxygen.

cm^{-1}); no carbonyl band was present. As in the case of **1a**, there were signals in the nmr spectrum of **2a** associated with a methylenedioxy group (δ 5.82), two para aromatic protons (δ 6.65), a methoxyl group (δ 3.47), and a proton on an oxygen-bearing carbon (δ 3.99) which was coupled to a benzylic proton (δ 3.45). The signal at δ 3.99 appeared as a broad triplet in $CDCl_3$ but collapsed to a sharp doublet when D_2O was added. Absence of any vinyl proton signals argued against the presence of a double bond in **2a**. A quartet appeared at δ 4.87 which was the X portion of an ABX system. Assuming that **2a** also had the cephalotaxine ring system, this signal was assigned to a proton on a carbon bearing both oxygen and aryl functions (C_{11}). An outstanding feature in the nmr spectrum of **2a** was the presence of two coupled (J = 14.0 Hz) one-proton doublets at δ 1.49 and 2.65. This coupling suggested that these were geminal protons in an isolated methylene group (C_1); no similar pair of doublets appeared in the spectrum of **1a**. Acetylation of **2a** gave a mono-*O*-acetyl derivative (**2b**, $C_{20}H_{23}NO_6$) demonstrating that **2a** contained only one hydroxyl group. The doublet at δ 3.99 in the nmr spectrum of **2a** shifted downfield to δ 4.78 in **2b**; however, the quartet at δ 4.87 was essentially unaffected. Thus the oxygen function assigned to C_{11} was necessarily involved in an ether-type linkage, and we concluded that the structure of **2a** could only be as shown. An alternative structure with an oxygen bridge between C_{10} and C_2 was considered unlikely from the nmr data and from inspection of molecular models.

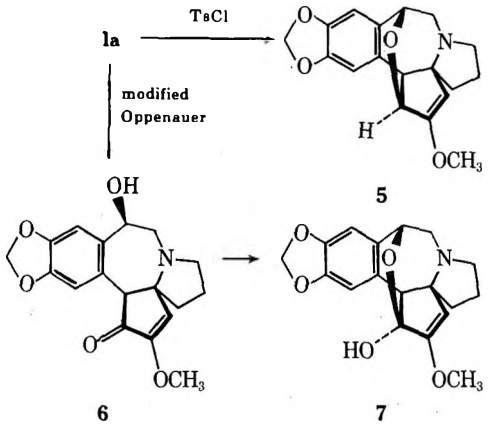
Alkaloid **2a**, for which we propose the name drupacine, can be regarded as a ketal formed by intramolecular addition of the C_{11} hydroxy group of **1a** to the double bond. McKay[3] reported an alkaloid (*Cephalotaxus* alkaloid G) with an nmr spectrum similar to that of **2a** although he did not assign a structure to it. In a recent paper, Asada[10a] reported an extensive reinvestigation of *Cephalotaxus* alkaloids including isolation of a compound (alkaloid IV) which he considers to be identical with McKay's alkaloid G.[10b] Neither of these workers appears to have encountered 11-hydroxycephalotaxine.

The structural relationship between **1a** and **2a** was confirmed by converting **1a** to **2a** under mildly acidic conditions; this conversion was essentially complete after 6 hr in 1.0 *N* hydrochloric acid at ambient temperature. In 5% tartaric acid, the reaction was approximately 5% complete in 1 hr and 50% complete in 24 hr. These observations suggest that a portion of **2a** from *Cephalotaxus* may be an artifact of isolation. However, it is unlikely that all of **2a** is formed in this manner since the time in contact with 5% tartaric acid was less than 2 hr during our isolation procedure. In order for such a reaction to occur, the configuration at C_{11} must be as shown in the accompanying stereoformula for **1a** (Figure 1). Molecular models reveal that a hydroxyl group at C_{11} is easily within bonding distance of C_2 and that the cage-like structure of **2a** is rigid but relatively unstrained. Models also demonstrate the close proximity of the C_3 and C_{11} hydroxyl groups of **1a** and explain the strongly hydrogen-bonded hydroxyl absorption noted in the ir spectrum.

We have confirmed the earlier observation that cephalotaxine (**3**) is resistant to catalytic hydrogenation.[3] In contrast, alkaloid **1a** was reduced to 11-hydroxy-1,2-dihydrocephalotaxine (**4**) in good yield with Adams catalyst in acetic acid. Under identical conditions, **1b**, **2a**, and **3** all gave no reaction. It is not apparent why the 11-hydroxyl group of **1a** should have such an accelerating effect on reduction. The configuration of the methoxyl group in **4** is uncertain although the nmr spectrum indicates that only one epimer is formed.

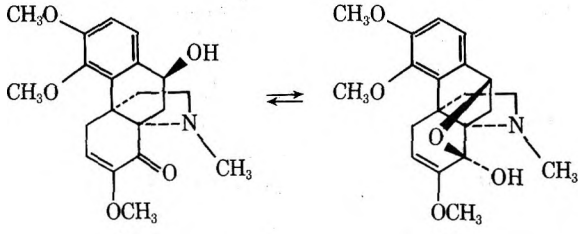
Previous experimentation had shown that the C_3 hydroxyl in cephalotaxine (**3**) is resistant to tosylation despite the fact that it is readily acetylated. We anticipated that the C_{11} hydroxyl in **1a** might be tosylated, leaving the C_3 hydroxyl unaffected and thus allowing removal of the C_{11} oxygen function by reduction with lithium aluminum hydride. However, when **1a** was treated with *p*-toluenesulfonyl chloride in pyridine, the only identifiable product was a cylic ether (**5**, $C_{18}H_{19}NO_4$). The structure of **5** was deduced from inspection of its ir (no hydroxyl or carbonyl), nmr, and mass spectra. Formation of **5** could be explained if an intermediate C_{11} tosylate or chloride

were the initial product. The chloride intermediate would most likely be inverted at C_{11} and consequently would be in a favorable position for back-side attack by the C_3 oxygen function to give the observed product. Similar chlorination reactions accompanied by inversion have been observed with methanesulfonyl chloride.[11,11a]

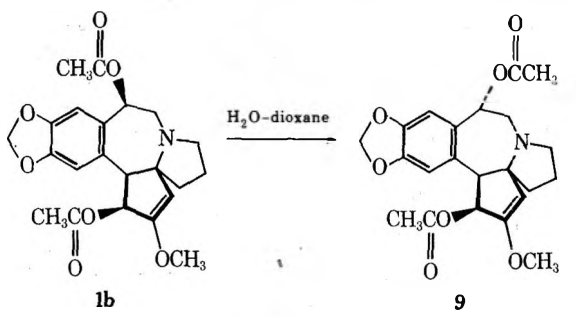


Oxidative approaches were also considered as a possible means of interconverting **1a** and **3**. Previous work had demonstrated that cephalotaxine is oxidized to cephalotaxinone by a modified Oppenauer procedure.[3,12] We applied this method to **1a** and obtained neither a dione nor **6** but instead isolated an abnormal product which was identified as 11-hydroxycephalotaxinone hemiketal (**7**). Although the nmr spectra of **5** and **7** were quite similar, the signal due to the proton on C_3 (d, δ 4.05) in **5** was absent in the spectrum of **7**, and the signal assigned to the proton on C_4 appeared as a singlet (rather than a doublet). Molecular models again demonstrated the rigid, but not highly strained, character of both **5** and **7**.

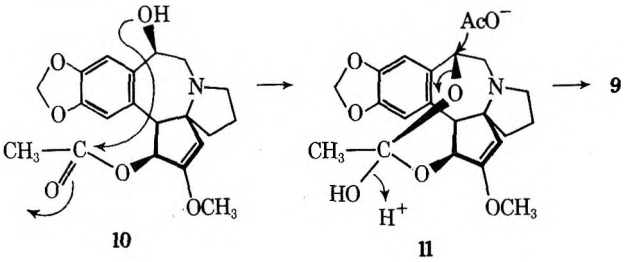
The relationship between compounds **6** and **7** is similar to that encountered with prometaphanine, which reportedly exists as an equilibrium mixture of a ketone (**8a**) and a hemiketal (**8b**).[13]



Slabaugh and Wildman[14] have reported the removal of a benzylic hydroxyl function in a successful conversion of 6-hydroxypowelline to powelline. The first step of their sequence involved a selective hydrolysis of 3,6-*O*,*O*-diacetylhydroxypowelline to 3-*O*-acetylhydroxypowelline at ambient temperature in dioxane–water. Following their procedure, we attempted selective hydrolysis of **1b** which gave an isomer (**9**) rather than the desired product, 3-*O*-acetylhydroxycephalotaxine (**10**). Compound **9** was easily



separated from the remaining **1b** by preparative tlc, and ir indicated that it contained no free hydroxyl groups. Mass spectra of **1b** and **9** were nearly identical. An nmr spectrum of **9** was similar to the spectrum of **1b** in that there were signals which could be attributed to two acetyl groups, a methoxyl group, a vinyl proton, a methylenedioxy group, and two aromatic protons. Also present was the characteristic pair of one-proton doublets due to the C_3 and C_4 protons (δ 5.72 and 3.58, J = 8.0 Hz). The chemical shift and coupling constant of the C_3 proton were nearly the same in both **1b** and **9** indicating that the configuration at C_3 had not changed. The vinyl proton signal had shifted downfield to δ 5.33 in the spectrum of **9**. A one-proton quartet at δ 6.34 was assigned to the C_{11} proton, and another quartet at δ 4.25 was assigned to one of the two C_{10} protons. These two protons were coupled, J = 11.0 Hz. Thus alkaloid **9** could only be the C_{11} epimer of **1b**. An acetate at C_3 is situated in an ideal position for transannular interaction with a C_{11} hydroxyl group formed in the hydrolysis. Although the mechanism of the epimerization is not known, S_N2 attack by the acetate ion on an ortho acid intermediate (**11**) could explain the results.



Other approaches to the interconversion of **1a** and **3** involved attempts to functionalize **3** at C_{11}. Oxidation of **3** under Étard conditions[15] gave a low yield of cephalotaxinone as the only recognized product. Reaction of **3** with *N*-bromosuccinimide,[16] in an attempt to brominate **3** selectively at C_{11}, again gave only cephalotaxinone; oxidation of alcohols is a well-known alternative reaction of *N*-bromosuccinimide.[17] Future attempts to functionalize **3** at C_{11} should be carried out on suitably blocked derivatives because the C_3 hydroxyl is quite sensitive to oxidation.

Conversion of **1a** to **2a** and to **5** and **7** leads us to conclude that the two hydroxyl groups can only be at C_3 and C_{11} with stereochemistry as shown. Examination of spectral data, molecular models, and considerations of possible mechanisms of formation of these products and of **9** all reinforce our structural assignment for **1a** which, incidentally, occurs as the most hindered of four possible geometric isomers. *C. harringtonia* var. *drupacea* is unique in containing these two alkaloids (**1a** and **2a**) not yet found elsewhere.[6,18]

Experimental Section

Melting points were determined on a Fisher-Johns[19] block and are uncorrected. A Beckman DK-2A spectrophotometer was used to record uv spectra, and ir analyses were done on 1% solutions in $CHCl_3$ with a Perkin-Elmer Model 137 instrument. Optical rotations were determined with a Cary Model 60 recording spectropolarimeter in 0.5-dm cells. Low-resolution mass spectra were obtained on a Du Pont (CEC) 21-492-1 spectrometer, and high resolution data with a Nuclide 12-90G spectrometer. Proton nmr spectra were measured with a Varian HA-100 instrument in $CDCl_3$ solution, and extensive spin decoupling was used to verify assignments.

All compounds and reaction mixtures were analyzed by tlc with appropriate solvent systems, normally $CHCl_3$–MeOH (9:1), on Brinkmann precoated 0.25-mm Silica Gel F-254 plates. Spots were visualized by staining the plates with iodine vapor. Preparative tlc separations were made on 1-mm Silica Gel G layers and

visualized with Bromothymol Blue. Samples were recovered from silica gel by washing with $CHCl_3$–MeOH (3:1), and all $CHCl_3$ extracts were routinely dried over anhydrous Na_2SO_4.

Isolation of Alkaloids. The general method for isolating crude alkaloid mixtures from *Cephalotaxus* plant material has previously been described in detail.[6] *Cephalotaxus harringtonia* var. *drupacea* (Sieb. + Zucc.) Koidzumi plants parts examined in this study included leaves, green twigs, woody stems, and seed.[20] Yields of crude alkaloid, expressed as percentages of total plant material, were as follows: leaf (0.15), twig (0.13), stem (0.12), and seed (0.81). Preliminary tlc of the leaf, twig, and stem samples indicated similar compositions with major amounts of alkaloids **1a** and **2a** along with lesser amounts of **3** and three minor unidentified materials. The seed sample contained several additional alkaloids.

A 1.0-g sample of crude alkaloid from twigs was separated on ten preparative tlc plates, which were developed with 15% MeOH in $CHCl_3$. This procedure gave alkaloids **1a** (280 mg), **2a** (290 mg), **3** (167 mg), and a mixture of unidentified materials (75 mg).

Preliminary separation of a 12.2-g sample of seed alkaloid was done by countercurrent distribution, and final separation of the individual alkaloids was carried out by a combination of column chromatography and preparative tlc. The entire procedure was described earlier.[6] Final alkaloid yields were as follows: **1a** (1.2 g), **2a** (1.9 g), and **3** (3.8 g). Two other alkaloids were positively identified by their mass and nmr spectra: harringtonine (0.8 g) and isoharringtonine (0.4 g).[8] A 3.3-g loss was encountered, most of which occurred during the column chromatographic step and left 0.9 g of unidentified material.

11-Hydroxycephalotaxine (1a). Alkaloid **1a** afforded colorless crystals from MeOH: mp 235–242° dec; $[\alpha]^{26}D$ −139° (*c* 0.56, $CHCl_3$); ir ($CHCl_3$) 3500 cm^{-1} (broad hydroxyl); nmr (Table I); mass spectrum (70 eV) *m/e* (rel intensity) 331 (100), 314 (61), 313 (39), 300 (24), 298 (39), 295 (36), 287 (24), 270 (59), 255 (25), 253 (21), 244 (22), 214 (24), 138 (24), 110 (22).

Anal. Calcd for $C_{18}H_{21}NO_5$: C, 65.24; H, 6.38; N, 4.22. Found: C, 65.41; H, 6.41; N, 4.23.

3,11-*O,O*-Diacetylhydroxycephalotaxine (1b). A 430-mg sample of **1a** was acetylated in 6 ml of acetic anhydride–pyridine (1:1) 18 hr at 26° and was then evaporated to a red-brown syrup on a rotary evaporator. The residue was dissolved in dilute NH_4OH, and products were recovered by $CHCl_3$ extraction. Crude product (443 mg) gave 265 mg of **1b** after preparative tlc on three plates (5% MeOH in $CHCl_3$). Alkaloid **1b** was obtained as a white amorphous solid: $[\alpha]^{26}D$ −168° (*c* 0.42, $CHCl_3$); uv max (C_2H_5OH) 289 nm (ϵ 3520), 237 (5830); ir ($CHCl_3$) 1740 cm^{-1} (ester carbonyl); nmr (Table I); mass spectrum (70 eV) *m/e* (rel intensity) 415 (10), 372 (7), 356 (30), 342 (100), 329 (4), 324 (3), 312 (5), 296 (11), 282 (5), 268 (6), 264 (5), 253 (5), 252 (5), 227 (5), 214 (9).

Drupacine (2a). Alkaloid **2a** afforded colorless crystals from a minimum solution of MeOH–$CHCl_3$ (1:1) to which a large excess of hexane had been added: mp 70–72°; $[\alpha]^{26}D$ −137° (c 0.79, $CHCl_3$); uv max (C_2H_5OH) 291 nm (ϵ 4090), 242 (3110); ir ($CHCl_3$) 3600 cm^{-1} (hydroxyl); nmr (Table I); mass spectrum (70 eV) *m/e* (rel intensity) 331 (88), 314 (10), 300 (26), 272 (10), 242 (14), 228 (23), 214 (14), 190 (84), 173 (14), 161 (73), 160 (14), 159 (20), 154 (41), 142 (100), 141 (48), 138 (38), 131 (16), 124 (28), 110 (31), 96 (18), 83 (36), 70 (18).

Anal. Calcd for $C_{18}H_{21}NO_5$: C, 65.24; H, 6.38; N, 4.22. Found: C, 65.55; H, 6.49; N, 4.13.

3-*O*-Acetyldrupacine (2b). A 53-mg sample of **2a** was converted to **2b** (47 mg) by the procedure cited for the preparation of **1b**. Acetate **2b** was obtained as an amorphous white solid upon evaporation of an ether solution under vacuum: mp 75–90°; $[\alpha]^{26}D$ +26° (c 0.23, $CHCl_3$); ir ($CHCl_3$) 1740 cm^{-1} (ester carbonyl); nmr (Table I); mass spectrum (70 eV) *m/e* (rel intensity) 373 (77), 356 (12), 330 (10), 314 (100), 254 (10), 242 (13), 228 (12), 214 (11), 190 (13), 189 (11), 173 (18), 172 (33), 161 (36), 154 (20).

Conversion of Hydroxycephalotaxine (1a) to Drupacine (2a). An 88-mg sample of **1a** in 10 ml of 1.0 *N* HCl was allowed to react at 26° for 6 hr. The reaction mixture was basified with Na_2CO_3 and then extracted repeatedly with $CHCl_3$. Preparative tlc of the crude product (91 mg) yielded 86 mg of **2a**: $[\alpha]^{26}D$ −62° (c 0.70, $CHCl_3$). The nmr, ir, uv, and mass spectra of **2a** produced in this manner were all indistinguishable from the corresponding spectra of naturally occurring **2a**.

In order to approximate acidic conditions encountered during isolation of the crude alkaloid mixture, 35-mg samples of **1a** were allowed to stand in 5% tartaric acid solution (26°) for periods of 1 and 24 hr, respectively. Products were recovered, after basification with ammonia, by extraction into $CHCl_3$. Under these conditions, conversion of **1a** to **2a** was approximately 5% complete in 1 hr and 50% complete in 24 hr, as judged by tlc.

Hydrogenation of Hydroxycephalotaxine (1a). A 53-mg sample of **1a** was hydrogenated at 26° and atmospheric pressure using Adams platinum catalyst in glacial HOAc (4 hr). Compound **4** (26 mg) was obtained by preparative tlc: ir ($CHCl_3$) 3400 cm^{-1} (broad hydroxyl); nmr (Table I); mass spectrum (70 eV) *m/e* (rel intensity) 333 (100), 318 (28), 302 (18), 274 (65), 245 (64), 244 (35), 228 (46), 227 (21), 214 (18), 188 (20), 140 (26), 128 (19), 126 (39), 112 (27), 96 (37). Under identical conditions, **1b**, **2a**, and **3** all gave no reaction.

Anal. Calcd for $C_{18}H_{23}NO_5$: M^+, *m/e* 333.158. Found: M^+, *m/e* 333.156.

Compound 5 from Attempted Tosylation of 1a. To a solution of 120 mg of **1a** in 5 ml of pyridine was added 177 mg of *p*-toluenesulfonyl chloride, and the resulting solution was allowed to react at 26° for 18 hr. Solvent was then evaporated under reduced pressure, the residue was dissolved in dilute NH_4OH, and 103 mg of crude product was recovered by ether extraction. Preparative tlc of the crude product yielded 19 mg of **5** along with 60 mg of a complex mixture of ill-defined materials. Compound **5** was an amorphous solid: $[\alpha]^{26}D$ +23° (c 0.18, $CHCl_3$), ir ($CHCl_3$) no hydroxyl or carbonyl bands; uv max (C_2H_5OH) 291 nm (ϵ 4460); nmr (Table I); mass spectrum (70 eV) *m/e* (rel intensity) 313 (100), 298 (26), 282 (8), 270 (9), 255 (10), 243 (10), 188 (14), 175 (25), 150 (16), 110 (22).

Anal. Calcd for $C_{18}H_{19}NO_4$: M^+, *m/e* 313.131. Found: M^+, *m/e* 313.129.

Oppenauer Oxidation of 1a and Recovery of 11-Hydroxycephalotaxinone Hemiketal (7). Alkaloid **1a** (129 mg), benzophenone (540 mg), and potassium *tert*-butoxide (86 mg) were dissolved in 25 ml of *tert*-butyl alcohol, and the solution was refluxed for 6 hr. Solvent was removed on a steam bath under a stream of N_2, the residue was dissolved in 5% HOAc, and the resulting solution was extracted with $CHCl_3$ to remove neutral or acidic materials. The remaining aqueous solution was basified with NH_4OH and extracted again with $CHCl_3$. Preparative tlc of the crude product (86 mg) gave 49 mg of **7** and 24 mg of unreacted **1a**. Compound **7** was an amorphous material: ir ($CHCl_3$) 3600 cm^{-1} (hydroxyl); nmr (Table I); mass spectrum (70 eV) *m/e* (rel intensity) 329 (100), 314 (18), 312 (22), 311 (13), 298 (17), 296 (22), 286 (25), 268 (19), 241 (15), 166 (15), 150 (45), 139 (77).

Anal. Calcd for $C_{18}H_{19}NO_5$: M^+, *m/e* 329.126. Found: M^+, *m/e* 329.126.

Attempted Selective Hydrolysis of 1b. A solution of 60 mg of **1b** in 10 ml of dioxane–water (1:1) was allowed to stand at room temperature for 72 hr. The solution was evaporated under reduced pressure, and chromatography of the crude product on a silica gel plate yielded 16 mg of unreacted **1b** and 21 mg of a new compound (**9**). The amorphous compound **9** gave no hydroxyl bands in the ir; nmr (Table I); mass spectrum (70 eV) *m/e* (rel intensity) 415 (5), 414 (6), 356 (11), 355 (6), 343 (19), 342 (100), 328 (8), 310 (6), 298 (5), 296 (6), 284 (6), 282 (5), 280 (5), 214 (6).

Anal. Calcd for $C_{22}H_{25}NO_7$: M^+, *m/e* 415.163. Found: M^+, *m/e* 415.164.

Oxidation of 3 with Chromyl Chloride. To a solution of 1.0 g of **3** in CCl_4 was added a solution of 0.3 ml of chromyl chloride in 5 ml of CCl_4. Considerable precipitate was formed immediately upon addition, and the mixture was allowed to stand for 3 hr. The precipitate was filtered and washed with CCl_4, yielding 285 mg of product. The precipitate was then dissolved in dilute aqueous NH_4OH, and the resulting solution was extracted repeatedly with $CHCl_3$ to yield an additional 500 mg of product. The recovered fractions appeared to be identical by analytical tlc and so they were combined; 400 mg of this mixture was separated by preparative tlc. This procedure yielded 21 mg of cephalotaxinone and 286 mg of unreacted **3**. These products were identical with known samples of the alkaloids as judged by ir, nmr, and mass spectra.

Reaction of 3 with *N*-Bromosuccinimide. To a solution of 200 mg of **3** in 6 ml of CCl_4 was added 115 mg of *N*-bromosuccinimide, and the resulting mixture was refluxed for 2 hr. Solids were then filtered and washed with $CHCl_3$. The filtrates yielded 237 mg of crude product which was then separated by preparative tlc. This procedure gave 68 mg of cephalotaxinone and 48 mg of unreacted **3**.

Acknowledgment. We thank Dr. R. E. Perdue, Beltsville, Maryland, for the collection of plant materials, Dr. D. Weisleder for nmr spectra, Mrs. C. E. McGrew for mi-

croanalyses, Mr. R. Kleiman and Dr. W. K. Rohwedder for mass spectra, and Dr. W. H. Tallent for valuable discussions of this work.

Registry No.—**1a**, 49686-55-7; **1b**, 49686-56-8; **2a**, 49686-57-9; **2b**, 49686-58-0; **3**, 24316-19-6; **4**, 49686-59-1; **5**, 49686-60-4; **7**, 49686-61-5; **9**, 49686-62-6.

References and Notes

(1) (a) Presented at the 166th National Meeting of the American Chemical Society, Chicago, Ill., Aug 26–31, 1973; (b) Agricultural Research Service, U. S. Department of Agriculture.
(2) W. W. Paudler, G. I. Kerley, and J. B. McKay, *J. Org. Chem.*, **28**, 2194 (1963).
(3) J. B. McKay, Ph.D. Thesis, Ohio University, Athens, Ohio (1966).
(4) W. Dallimore and A. B. Jackson, "Handbook of *Coniferae*," Longmans Green and Co., New York, N. Y., 1923, pp 20–23.
(5) W. Dallimore and A. B. Jackson, revised by S. G. Harrison, "A Handbook of Coniferae and Ginkgoaceae," St. Martin's Press, New York, N. Y., 1967, pp 146–152.
(6) R. G. Powell, *Phytochemistry*, **11**, 1467 (1972).
(7) R. G. Powell, K. L. Mikolajczak, D. Weisleder, and C. R. Smith, Jr., *Phytochemistry*, **11**, 3317 (1972).
(8) R. G. Powell, D. Weisleder, and C. R. Smith, Jr., *J. Pharm. Sci.*, **61**, 1227 (1972).
(9) R. G. Powell, D. Weisleder, C. R. Smith, Jr., and I. A. Wolff, *Tetrahedron Lett.*, 4081 (1969).
(10) (a) S. Asada, *Yakugaku Zasshi*, **93**, 916 (1973). (b) The nmr spectra of McKay's alkaloid G, Asada's alkaloid IV, and our alkaloid **2a** show most of the same major peaks with only minor differences in some of the reported chemical shifts. Strikingly similar are the two doublets (δ 1.44 and 2.64, J = 14.0 Hz) attributed to an isolated methylene group. However, there are considerable differences in the melting points of our sample of **2a** (70–72°), Asada's alkaloid IV (80–82°), and McKay's alkaloid G (131–131.5°). The nmr spectra of the acetate derivatives of all three samples are also nearly identical.
(11) J. S. Fitzgerald, S. R. Johns, J. A. Lamberton, and A. A. Sioumis, *Aust. J. Chem.*, **22**, 2187 (1969).
(11) (a) Note Added in Proof. It has come to our attention that a sesquiterpenoid polyol, euonyminol, undergoes an analogous ether-forming reaction when treated with tosyl chloride [*cf.* M. Pailer, W. Streicher, and J. Leitich, *Monatsh. Chem.*, **102**, 1873 (1971).]
(12) R. G. Powell and K. L. Mikolajczak, *Phytochemistry*, **12**, 2987 (1973).
(13) M. Tomita, T. Ibuka, and Y. Inubushi, *Tetrahedron Lett.*, 3617 (1964).
(14) M. R. Slabaugh and W. C. Wildman, *J. Org. Chem.*, **36**, 3202 (1971).
(15) W. H. Hartford and M. Darrin, *Chem Rev.*, **58**, 1 (1958).
(16) D. J. Cram and G. S. Hammond, "Organic Chemistry," McGraw-Hill, New York, N. Y., 1959, p 431.
(17) R. Filler, *Chem. Rev.*, **63**, 21 (1963).
(18) R. G. Powell, unpublished observations.
(19) Mention of trade or manufacturer's name is not a recommendation or endorsement by the U. S. Department of Agriculture over those not mentioned.
(20) Leaf and stem samples were collected from a tree in Maryland during Nov 1968. The seed sample came from Italy in 1962.

Oxymercuration–Demercuration of Limonene

Massimo Bambagiotti A.,* Franco F. Vincieri, and Silvia A. Coran

Istituto di Chimica Farmaceutica, Università degli Studi di Firenze, 50121 Florence, Italy

Received August 14, 1973

The oxymercuration–demercuration procedure, in aqueous THF, was applied to limonene (**1**) to investigate the behavior of its two double bonds. It was shown that *cis*-1,8-terpin (*cis*-**7**) and 1,8-cineole (**9**) were produced when a 1:2 limonene–$Hg(OAc)_2$ mole ratio was used. Production of α-terpineol (**5**) together with *cis*-**7** and **9** was observed when the limonene–$Hg(OAc)_2$ mole ratio was reduced (1:1 and 1:0.5). The reactions were very fast and no oxidative side process was evident. Further information on the reactivity of the endocyclic limonene double bond was given by comparison of the behavior of **5** and 1-*p*-menthene under the same reaction conditions. The results indicate that the first hydroxyl group that adds onto the external limonene double bond enhances the reactivity of the internal double bond, promoting a high overall reaction rate. Moreover, the unexpected production of both *cis*-**7** and **9** indicates that, although the first hydroxyl group is in an ideal position to react, *via* a six-membered ring, to give the corresponding cyclic ether **9**, the latter only partially forms, the major product being the corresponding diol *cis*-**7**.

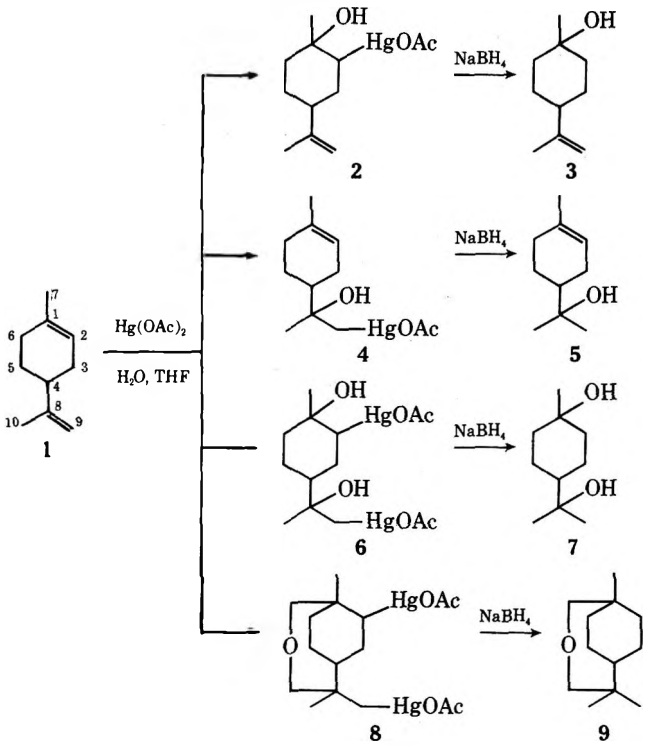
We undertook the present study in order to investigate the relative reactivity of the two differently hindered unconjugated double bonds of limonene, with respect to the mercuric acetate addition, as part of a program which involves the combined use of mercuric acetate addition and tlc as a qualitative analytical tool for the monoterpene hydrocarbon class.[1] The isolation for identification purposes of the hydroxymercurials obtained carrying out the addition reactions in aqueous medium, appeared to be a matter of considerable difficulty. We then monitored the reactions *via* the isolation and identification of the products obtained by reduction of the mercuric adducts with $NaBH_4$, according to Brown's procedure.[2] This consists of an oxymercuration–demercuration sequence which provides, in this case, a convenient method of obtaining known monoterpene alcohols, easily detectable by glpc.

Results and Discussion

The following oxymercuration–demercuration scheme might result if account is taken of both reaction sites on the limonene molecule (Scheme I).

The reaction carried out in a 1:2 limonene–mercuric acetate molecular ratio was very fast,[3] coming to completion in a matter of seconds. Analysis for alcohols, after reduction, showed an almost quantitative yield of *cis*-1,8-terpin (*cis*-**7**) (hydrate) and 1,8-cineole (**9**). This implies that the endo- and exocyclic double bonds, despite the different steric hindrance, show a similar high reactivity. On the other hand, a considerable difference in reactivity should have promoted a sequence in the mercuration stage, most likely initially involving the external double bond and then the internal one after the first attack arrived at completion. Accordingly, running a reaction in a 1:1 limonene–mercuric acetate molecular ratio, would give rise to the adduct **4** as the major product which, on reduction, leads to α-terpineol (**5**), while β-terpineol (**3**), *cis*- or *trans*-**7** and **9**, which originate respectively from **2**, **6**, and **8** adducts, should be absent or present in only very small amounts. On the contrary, a high yield of *cis*-**7** (hydrate) and **9**, together with the expected **5**, was observed carrying out this 1:1 reaction, which was complete in the same time as the 1:2 ratio reaction. Obviously a corresponding amount of unreacted limonene was also found. The same situation concerning both products and rate was also observed running a 1:0.5 limonene–mercuric acetate reaction. It should be emphasized that the reactions were ex-

Scheme I



tremely smooth under the standard experimental conditions and that no side oxidation process was evident even when an excess of mercuric salt was used (1:4).

From these results it was apparent that in the adduct 4 the reactivity of the endocyclic double bond was so tremendously enhanced as to compete favorably with the external limonene double bond.

To support this point of view we then explored the effect of oxymercuration on 1-*p*-menthene to ascertain the reaction rate of its endocyclic double bond. Under the standard operative conditions (1:1), the reaction was markedly slower with respect to limonene and, even in 30 min, the yield of alcohol was not quantitative. This made it evident that the limonene trisubstituted double bond, although seemingly comparable with that of 1-*p*-menthene, displayed more reactivity than expected. We therefore thought that the factor which might influence the overall reaction rate might be the presence of the exocyclic unsaturation in the limonene molecule. Assuming that mercuric salt attack took place primarily on this double bond, leading to the adduct 4 at an extremely high rate, the subsequent reactivity increase of the endocyclic double bond, leading to the adduct 4 at an extremely high oxymercuration elements (hydroxyl group and acetomercury group) or, more simply, only to the hydroxyl group in position 8.

In order to test these hypotheses, a reaction on α-terpineol was made using standard conditions in a 1:1 reagent ratio. The observed rate was as high as for limonene and a 2-min reaction time was sufficient to obtain an almost quantitative yield of *cis*-7 and 9 in relative amounts comparable to those from limonene.[4,5]

It must be noted that, in an early paper, Sand, *et al.*,[6] and most recently Brook, *et al.*,[7] reported the production of 9 and *trans*-7, without trace of its cis isomer, when the oxymercuration of α-terpineol was carried out with mercuric nitrate in a heterogeneous aqueous medium. However, applying the standard borohydride reduction procedure to the adducts obtained by Sand's method, we found that *cis*-7 was formed together with the trans isomer ($\simeq$1:2 relative ratio). 1,8-Cineole (9) was also present. See Table I.

Table I
Summary of Oxymercuration–Demercuration Reactions

Compd	Compd/ $Hg(OAc)_2$	Reaction products,[a] % 1	5	*cis*-7	*trans*-7	9
1	1:2		3.2	72.2		24.6
1	1:1	30.5	35.1	26.0		8.4
1	1:0.5	68.3	15.5	13.0		3.2
5[b]	1:1		2.2	68.6		29.2
5[c]	1:1		22.4	20.2	48.8	8.6

[a] Calculated by taking the sum of glpc peak areas as 100. [b] Standard procedure. [c] Sand, *et al.*, modified procedure.

In conclusion, the overall results of this study reveal that, in the oxymercuration of limonene, the first hydroxyl group to enter influences the successive introduction of the mercuration elements on the endocyclic double bond by enhancing the corresponding reaction rate, so that the two 1,2-Markovnikov additions did not occur as competitive steps.

The operative reaction conditions play a decisive role on the adduct sterochemistry. The procedure used displays high stereospecificity leading only to the cis isomer of terpin while the earlier procedures, in heterogeneous medium, give rise to both cis and trans isomers.

Although it was observed that the possibility of formation of five- or six-membered cyclic ethers promotes an almost quantitative yield of these with respect to the corresponding diols,[8] in the present case limonene gives rise to considerable amounts of both types of products. This suggests that both the 8-hydroxyl internal group and water act as competitive nucleophiles with respect to the 1 position during oxymercuration and that neither of the two fully predominates.

Experimental Section

Materials. Limonene (1) and 5 were obtained commercially and purified before use by preparative glpc. 1-*p*-Menthene was prepared by sodium amyl alcohol reduction of α-phellandrene. The procedure was essentially identical with that described by Semmler[9] except for the removal of the excess amyl alcohol, which was performed by column chromatography over silica gel, using *n*-hexane as eluent. From the eluate 1-*p*-menthene was isolated by preparative glpc using a 2.7 m × 7.8 mm i.d. column packed with 20% Carbowax 20M on Chromosorb A, 60–80 mesh, 80–160°, 3°/min. The ir spectrum was identical with that reported in the literature.[10] *trans*-7 was obtained according to Baeyer's method.[11] All chemicals and solvents were reagent grade and used as obtained.

Oxymercuration–Demercuration Reactions. Limonene (1). Limonene (10 mmol) was added under stirring to the solvent system (10 ml H_2O + 10 ml THF) containing 20 mmol of $Hg(OAc)_2$, to perform the 1:2 mole ratio reaction. Mercuric acetate (10 mmol or 5 mmol) was employed in the 1:1 or 1:0.5 mole ratio reactions under the same conditions. The disappearance of the yellow suspension which formed when THF was added to the aqueous solution of $Hg(OAc)_2$ was used to monitor the reaction rate.[2] The time required was 7–10 sec in all cases; hence, all reactions were allowed to proceed for the same time period (2 min) before initiating the reduction. This was performed using 20, 10, or 5 ml of both 3 *M* NaOH and a 0.5 *M* solution of $NaBH_4$ in 3 *M* NaOH for the 1:2, 1:1, or 1:0.5 mole ratios, respectively. After stirring until all the mercury had coagulated, the aqueous layer was saturated with K_2CO_3 and the upper THF layer separated. The aqueous phase was again extracted twice with 10-ml portions of THF. The combined THF extracts were then dried over anhydrous K_2CO_3.

1-*p*-Menthene. The reaction, carried out in standard conditions in a 1:1 reagent ratio, required 3 min for the disappearance of the yellow suspension. A time period of 30 min was then allowed to elapse before reduction.

α-Terpineol (5). Standard Procedure. α-Terpineol (5) and $Hg(OAc)_2$ (both 10 mmol) were allowed to react under standard conditions to perform a 1:1 reaction. Since the yellow suspension vanished in 7 sec, the reaction was allowed to continue for 2 min.

α-Terpineol (5), Modified Sand Procedure. The original method[6] was exactly followed for the oxymercuration stage using 10 mmol of reagents (2.16 g of HgO and 1.54 g of **5**). When the addition was complete, the subsequent reduction was performed by the standard procedure adding 10 ml of 3 *M* NaOH and 10 ml of 0.5 *M* $NaBH_4$ in 3 *M* NaOH to the reaction mixture and extracting with THF as stated above.

Analyses. Qualitative and quantitative analyses were made by glpc. After evaluation of several types of glpc columns, the best choice was a 3 m × 3.5 mm i.d. glass column packed with 5% QF-1 on Anakrom ABS, 90–100 mesh (10 min at 80–170°, 3°/min), which also worked well for the separation of **9** from **1**. The dried THF extracts were gas chromatographed and the reaction products identified by comparison of their retention times with those of authentic samples. On the other hand, column chromatography on silica gel (Merck, 200 mesh ASTM) was found adequate for isolation of **1**, **9**, and **5**, eluting with a benzene–ethyl acetate 40:60 mixture. Subsequent elution with methanol drew *cis*-**7**. In this case all these compounds were identified by ir spectroscopy after purity checks carried out by glpc and tlc on Merck silica gel G with various solvent systems.

Quantitative determinations were performed by glpc peak area evaluation using a Perkin-Elmer SIP-1 electronic integrator. Calculation of relative weight percentages required the determination of relative detector (FID) response factors from a THF standard solution of known amounts of **1**, **9**, **5**, and *cis*-**7**. Each reaction was repeated to ascertain quantitative reproducibility, and percentages in the text represent average results. In every case reproducibility was within ±1.5%.

Acknowledgments. The support of the Cap.XI/b, Consiglio di Amministrazione dell'Università degli Studi di Firenze, is gratefully acknowledged. The authors would also like to thank Dr. G. Mazzi for assistance in the experimental work.

Registry No.—**1**, 138-86-3; **5**, 10482-56-1; $Hg(OAc)_2$, 1600-27-7.

References and Notes

(1) M. Bambagiotti A., F. F. Vincieri, and G. Cosi, *Phytochemistry*, **11**, 1455 (1972).
(2) H. C. Brown and P. J. Geoghegan, *J. Org. Chem.*, **35**, 1844 (1970).
(3) All statements about reaction rates refer to grossly observed relative rates as described in the Experimental Section.
(4) Coxon, *et al.*,[5] stated that the oxymercuration of **5** in the presence of water followed by reduction under Brown's conditions gave terpine hydrate, with no mention of **9**.
(5) J. M. Coxon, M. P. Hartshorn, J. W. Mitchell, and K. E. Richards, *Chem. Ind. (London)*, 652 (1968).
(6) J. Sand and F. Singer, *Ber.*, **35**, 3170 (1902).
(7) A. G. Brook and G. F. Wright, *J. Org. Chem.*, **22**, 1314 (1957).
(8) H. C. Brown, P. J. Geoghegan, Jr., J. T. Kurek, and G. J. Lynch, *Organometal. Chem. Syn.*, **1**, 7 (1970–1971).
(9) F. W. Semmler, *Ber.*, **36**, 1033 (1903).
(10) B. M. Mitzner, E. T. Theimer, and S. K. Freeman, *Appl. Spectrosc.*, **19**, 169 (1965).
(11) A. Baeyer, *Ber.*, **26**, 2861 (1893).

Reaction of Terpenes with Diethyl Phosphonate under Free Radical Conditions

Robert L. Kenney and Gordon S. Fisher*[1a]

Naval Stores Laboratory,[1b] Olustee, Florida 32072

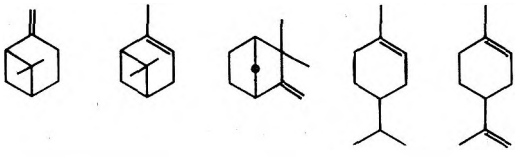
Received September 11, 1973

β-Pinene (**1**), α-pinene (**2**), camphene (**3**), carvomenthene (**4**), and limonene (**5**) were treated with commercial diethyl hydrogen phosphite to yield phosphonates. The phosphonate addition to the pinenes yielded *p*-menthenyl derivatives, to camphene yielded isocamphanyl derivatives, and to limonene yielded diphosphonates, with a bornyl derivative as a minor product. Structures based on ir and nmr data are discussed.

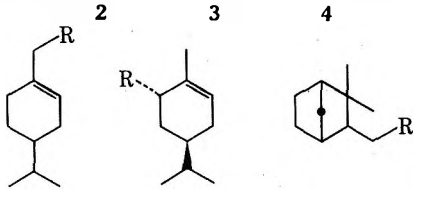
As part of this laboratory's efforts to produce flame-resistant naval stores derivatives, it was of interest to prepare some terpenyl phosphonic acids or phosphonates.

The preparation of alkyl phosphonates from olefins has been studied to some extent. Pudovik and Konovalona[2] used uv light or benzoyl peroxide to effect 1:1 anti-Markovnikov addition of dialkyl phosphonates to unsaturated hydrocarbons. They noted that telomers and polymers also were formed. Stiles, *et al.*,[3] obtained polymers when peroxides were used to initiate the addition of dialkyl phosphonates to olefins. Recently, Callot and Benezra,[4] using benzoyl peroxide, added dimethyl phosphonate to norbornadiene to yield a norbornene phosphonate, two diphosphonate derivatives, and a nortricyclene derivative.

In this study we treated commercial diethyl hydrogen phosphite (DEHP) with β-pinene (**1**), α-pinene (**2**), camphene (**3**), carvomenthene (**4**), and limonene (**5**) in the presence of di-*tert*-butyl peroxide (DTBP). From **1** a 94% yield of a single product (**6**) was obtained. The elemental analysis established that it was a 1:1 adduct. The presence of a P=O absorption[4] at 1245 cm^{-1} in its infrared spectrum showed that the terpenyl linkage was to the phosphorus, as expected, not to the oxygen. The appearance of a broad olefinic proton peak at 5.53 ppm in the nmr spectrum showed that the addition had been accompanied by ring opening, as in the case of other free radical additions to β-pinene.[5] The other features of the nmr spectrum were in accord with this assignment. It should be noted that the C_7-H_2 resonance at 2.16 ppm was deshielded by only about 0.2 ppm from the normal allylic methylene position[6] by the phosphonate group. As previously reported,[7] the ethoxy methylene was a quintet due to equal coupling to the methyl protons and to phosphorus.



1 **2** **3** **4** **5**



6 **7** **8**

R = $PO(OCH_2CH_3)_2$

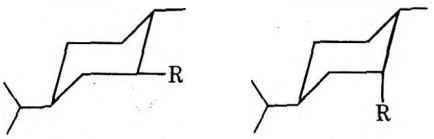
A single product (**7**) was also obtained from **2**, but the yield was somewhat lower (56%). As with **6**, elemental analyses and infrared spectrum indicated that it was a ring-opened 1:1 adduct. On steric grounds, the phosphonyl radical should attack **2** trans to C_6 leading to **7**. This configuration was confirmed by the high molecular rotation of

the product,[8] which also strongly supports an equitorial isopropyl conformation. Again the effect of the phosphonate group on chemical shifts is of interest. The vicinal, allylic methyl group was deshielded by about 0.15 ppm, but the protons common to 6 and 7 had essentially the same shielding. The deshielding effect of the phosphonate group on the C_6-methine proton was difficult to evaluate, but appeared to be of the same order of magnitude as its effect on the C_7 methylene protons in 6.

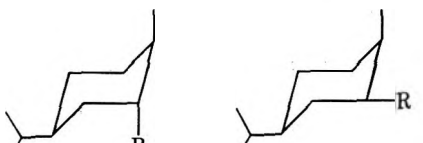
Compound 3 gave a 97% yield of a mixture of two isomers ($\alpha_{2:1}$ = 1.07) in a ratio of about 1:3 in order of emergence. The major isomer was isolated in about 90% purity by preparative gas chromatography (pgc). Davis, *et al.*,[9] added thiophenol to 3 under radical conditions and reported only the *endo*-isocamphanyl product, but they pointed out that with bulkier reagents both exo and endo products should be formed. In no case did they observe skeletal rearrangement of the norbornane ring. On this basis, the major product in the present case should be the *endo*-isocamphanyl phosphonate (8) and the minor one the exo epimer. The nmr spectrum supported the assignment of 10-camphanyl structures to both isomers. In particular, the difference in chemical shift between the geminal methyl groups of each isomer precluded a rearranged 10-bornyl structure. However, complexity of the low field region (five protons between 1.7 and 2.5 ppm) and the fact that both the cis and the trans methyls[10] of the major isomer were more shielded than the corresponding methyls of the minor isomer precluded any steric assignment based on the nmr spectrum.

In any case, much more endo transfer occurred with DEHP than with benzenethiol. The difference can be rationalized on the basis that the steric requirements of the diethylphosphonyl radical (or attached group) are greater than those of the phenylthioyl group, making the endo configuration less favorable, but that, because of the greater length of the P–H bond, steric requirements in the transfer step are less for the DEHP, permitting more endo transfer. Alternatively, it is reasonable that exo addition of the phosphonate radical at C_{10} will be favored leading to the less crowded endo C_3 radical, some of which will be trapped if diethyl phosphonate is a better transfer agent than the thiol.

The product obtained from 4 was an even more complex mixture. Analytical glc gave one major peak bracketed by two minor peaks and a fourth very minor peak with much shorter emergence time. Preparative glc readily separated the minor isomer with the longest retention time, but the other minor peak was difficult to separate. By analogy to results of other radical additions to 1,4-dialkylcyclohexenes,[11] the major product should be the neocarvomenthyl phosphonate (**9b**). The neighboring peaks should be the



9a **9b**



9c **9d**

R = $PO(OCH_2CH_3)_2$

carvomenthyl (**9a**) and neoisocarvomenthyl (**9d**) isomers. The infrared spectra of these three were very similar while that of the early peak was different. This supported assignments of diastereoisomeric structures to the three largest peaks and a different structure (*i.e.*, not **9c**) to the early peak.[12] The nmr spectrum of the last glc peak indicated that it was a single isomer with one $POCH_2$ quintet and one C_1-methyl doublet, slightly broadened by long range coupling with phosphorus. On the other hand, the nmr spectrum of the last two thirds of the major peak[13] exhibited two doublets for C_1 methyl and two quintets for methylene protons of the diethyl phosphonate group. Ratios of the corresponding peak heights for the two patterns fall in the range of 35:65 to 40:60, clearly indicating that this glc peak was a mixture of two isomers and that all four isomers of 9 were formed.

Heteronuclear decoupling of both samples confirmed the assumption that the abnormal multiplicity of the OCH_2CH_3 resonance was due to vicinal coupling with phosphorus[7] and sharpened the C_1-methyl bands enough to permit estimation of the methyl–methine coupling (J) for each isomer. Among the carvomenthols, J = 7 Hz for the 1-methyl of neoisocarvomenthol[14] and 6 Hz or less for the 1-methyl of the other three. Since in the present case J = ~6 Hz for the 1-methyl of both major isomers and 7 Hz for the isomer with the longest retention time, this isomer was assigned structure **9d**. The fact that neoisocarvomenthol also has a longer retention than its diastereomers[15] supports this assignment. A similar rationale based on optical rotation can be used to assign structure **9a** to the first minor peak. With C_4 fixed in the *R* configuration, carvomenthol is levorotatory. The other three isomers are dextrorotatory.[15,16] The agreement in molecular rotation [M_D] between 7 and *trans*-carvotanacetol[8] indicated that the hydroxyl group and phosphonate group make similar contributions to the molecular rotation, so only **9a** should be levorotatory. Although it was not practical to get enough of the first minor peak to determine its optical rotation, a reasonably accurate value could be calculated. A glc cut containing 35% of this isomer and 65% of the major peak (M_D = 45°) had M_D = 18°. This corresponds to M_D = −32° for the minor component, compared to M_D = −40° for carvomenthol.[15] Hence, this minor product was **9a** and the major peak was a mixture of **9b** and **9c**.

Rigorous interpretation of the nmr spectral differences in terms of structure was not feasible, but a tentative assignment of structure **9b** to the higher field isomer was made on the basis of the $POCH_2$ resonances. The resonances of the more abundant isomer and **9d** were nearly identical, but the less abundant isomer resonated at higher field. This can be rationalized by assuming that the resonance is determined by the conformation of the $POCH_2$. This group is certainly bulkier than OH; so **9c** should be predominantly the equatorial $POCH_2$ conformer[17] and would have the same resonance as **9d**. The different resonance would belong to the axial $POCH_2$ of **9b**. On this basis, in a typical product the ratio of **9a:9b:9c:9d** would be 8:32:49:11.

The most striking difference between these results and those obtained with 4-*tert*-butyl-1-methylcyclohexene and thiolacetic acid[11] was the formation of **9c** as the major product. None of the corresponding thiolacetate was formed. Radical attack trans to the isopropyl still accounted for 80% of the product, so the difference represented less selectivity in the hydrogen transfer step. This difference is most readily explained on the basis that the C_1 radical is pyramidal[18] and that hydrogen transfer occurs axially.[11] With the relatively small thiolacetate group and the very bulky *tert*-butyl group, the intermediate radical is effectively locked in the original 1-e,2-a,4-e conformation, which is retained after axial hydrogen transfer. Effectiveness of the transfer agent is not involved in the

Table I
Retention Times (Minutes) of Phosphonates on Various Columns[a]

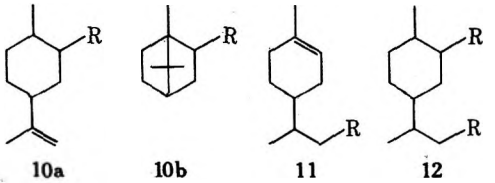
	Temp, °C	He, ml/min	9a	9b,c	9d	7	6
3/16 in. × 12 ft × 20% Carbowax 20M	230	63	15.0	16.0	19.1	16.1	29.2
3/16 in. × 12 ft × 5% Carbowax 20M	230	60	3.1	3.3	3.9	3.4	6.0
3/16 in. × 12 ft × 7.5% Versamid-900	230	67	5.0	5.5	6.3	4.9	9.0
1/4 in. × 15 ft × 10% Versamid-900	220	100	5.7	6.2	7.2	5.2	9.8
1/4 in. × 15 ft × 15% Carbowax 20M	225	100	18.9	20.4	21.5		
1/4 in. × 15 ft × 20% SE-33[b]	235	120	20.9	22.9	24.7		
1/4 in. × 20 ft × 10% SE-33	230	100	12.3	13.1	14.7		
1/4 in. × 20 ft × 20% OV-17	225	120	22.2	24.3	27.7		
1/4 in. × 20 ft × 10% SE-30	220	75	15.1	16.0	17.9		

[a] The 3/16 in. columns were used on the Varian 1200 and the retention times were measured from the leading edge of the solvent peak (cyclohexane). The 1/4 in. columns were used on the Wilkens Autoprep-700 and the measurements were from the air peak. All packings were on 70–80 mesh Chromsorb W. [b] Support coated with 1% alkaline Carbowax 20M.

specificity. In the present case, the phosphonate group is at least as bulky as the isopropyl group; so inversion to the 1-e,2-e,4-a conformation, leading to the stable conformer of **9c**, can occur. The product ratio will be influenced by the general effectiveness of the transfer agent, relative stabilities of the two radicals, and any differences in crowding during the transfer step. We can only say that the equilibrium favored the precursor of **9c** and that the phosphonate was not active enough to trap a high percentage of the initial radicals.

The ratios of the isomers arising from attack cis to the isopropyl group were also quite different in the two systems. Paradoxically, less inversion occurred in the carvomenthene-phosphonate system. As has been pointed out by others,[11] attack from the cis face of the molecule does not form an equatorial bond but rather a quasiaxial bond on a flexible skew-boat ring. Hydrogen transfer trans to the point of radical addition also involves a quasiaxial position, somewhat like the endo position in norbornanes and gives compounds like **9d**. The cis 2,4 substituents preclude any conformation of the skew-boat which would give **9a** structures by quasiaxial (or flagstaff) hydrogen transfer. On the other hand, inversion to the chair form followed by axial hydrogen transfer will give only 1-e,2-e,4-e conformations like **9a**. If, as suggested in discussing the addition to **4**, diethyl phosphonate is a better transfer agent than a thiol, more transfer to the flexible radical should occur. This would result in a greater proportion of **9d**, as was observed. Molecular models indicate that an isopropyl group does not restrict the flexibility of the skew-boat as much as a *tert*-butyl group does. This may also contribute to the higher yield of 9d by increasing the life of the skew-boat radical.

Using the standard reaction conditions, compound **5** gave a mixture of 1:1 and 1:2 adducts. Due to the dimerization of **5**, efforts to get only the 1:1 adducts by using reverse addition to maintain a large excess of **5** were unsuccessful, but nearly quantitative yields of 1:2 adducts were obtained by adding more peroxide and increasing the reaction time. The nmr spectrum of the major 1:1 adduct



10a **10b** **11** **12**

R = $PO(CH_2CH_3)_2$

established its structure as **11**. Quantitative hydrogenation confirmed the presence of one double bond.

On the basis of its nmr spectrum and its failure to hydrogenate, the minor (shorter emergence time) 1:1 adduct was not **10a** but a saturated product. The nmr spectrum exhibited 6- and 3-proton singlets and a broad 1-proton doublet at 2.22 ppm (J = 17 Hz), presumably due to a PCH methine slightly coupled to other hydrogens. These spectral features require a structure such as **10b**. Since the exocyclic double bond reacted much more rapidly than the endo one, any **10a** formed would have been converted rapidly to **12**. So failure to build up any significant concentration of **10a** is not surprising. When a crude product that was mostly 1:1 adducts was hydrogenated, the early peak decreased and an equivalent amount of a peak corresponding to **9b,c** appeared. Hence, **10a** was present in the crude product and had the same emergence time as **10b**.

The nmr spectrum confirmed that the material with long retention time contained two phosphonate groups per mole of **5**. As in the case of **9**, all four isomers were obtained. No attempt was made to isolate and identify the individual isomers, but it is assumed that **12a** and **12d** have structures corresponding to **9a** and **9d**.

Formation of **10b** from **5** was unexpected, but it is reasonable. As in the case of **4** and **11**, the radical attack at C_2 of **5** trans to the isopropyl group should predominate. As previously discussed, formation of **9c** and **12c** demonstrated that some inversion of the initial radical at both C_2 and C_4 occurred faster than hydrogen transfer. Stepwise inversion leads to a flexible boat structure. One conformation of this boat places the partially filled p or sp_3 orbital at C_1 close to the π bond at C_8 and reasonably well aligned for overlap leading to s-bond formation. This would generate an unhindered radical, at C_9, that would pick up a hydrogen to give **10b**. On this basis, **10b** would have an exo methine hydrogen at C_2; *i.e.*, it should be the bornyl phosphonate. This assignment was confirmed by the molecular rotation (+52°). (+)-Limonene is structurally related to (+)-borneol (M_D = +58°) and to (−)-isoborneol.[19]

In order to determine whether the phosphonate derivatives would have significant flame retardance, pieces of filter paper were saturated with 10% solutions of each adduct, drained, and air-dried. The coated strips were mounted vertically and a lighted match was touched to the top edge. In general, the strips would ignite but would not sustain a flame.

Experimental Section

The terpenes and diethyl hydrogen phosphite (DEHP) used were freshly distilled from commercial samples.[20] Densities were determined in calibrated hairpin glass capillaries. Optical rotations were determined neat. Ir curves were run neat on a Perkin-Elmer, Model 21 infrared spectrophotometer. Nmr was determined in deuteriochloroform ($CDCl_3$) with tetramethylsilane (TMS) as an internal standard using Varian A-60A and Bruker 90-MHz instruments. Elemental analyses were carried out by Galbraith Laboratories, Inc., Knoxville, Tenn.

Table II
Nmr[a] Chemical Shift (Parts per Million), Multiplicity, and Coupling Constant (Hertz)

Isomer	$C_{9,10}$–CH_3	C_7–CH_3	$POCH_2$	$POCH_2CH_3$
9b,c (major)	0.89 (d, J = 6)	1.15 (d, J = 6)	1.32 (t, J = 7)	4.10 (qn, J = 7)
Decoupled[b]	0.90 (d, J = 6)	1.17 (d, J = 7)	1.34 (t, J = 7)	4.10 (q, J = 7)
9b,c (minor)		1.11 (d, J = 5)		4.08 (qn, J = 7)
Decoupled[b]		1.13 (d, J = 5)		4.09 (q, J = 7)
9d	0.91 (d, J = 6)	1.08 (d, J = 7)	1.33 (t, J = 7)	4.10 (qn, J = 7)
Decoupled[b]	0.92 (d, J = 6)	1.08 (d, J = 7)	1.34 (t, J = 7)	4.11 (q, J = 7)

[a] At 90 MHz, in $CDCl_3$ (J values in Hz). [b] p31 at 6342 Hz.

Table III
Composition, %[a]

Hr	10	11	12	Total
0.5	1.2	4.2	1.7	7.0
1.0	2.1	6.5	1.8	10.4
2.0	2.7	8.6	5.6	16.9
3.5	2.4	9.4	9.2	21.0
4.5	2.2	5.0	22.4	29.6
6.25	2.0	0.1	32.1	34.2

[a] Per cent of reaction mixture.

General Procedure. Adducts were prepared by heating 0.5 mol of DEHP to 140°, adding 0.005 mol of di-*tert*-butyl peroxide (DTBP), then adding 0.1 mol of terpene dropwise over a period of about 30 min and continuing heating for a total of 3.5 hr. Most of the unreacted materials were distilled off under vacuum. An ether solution of the residue was extracted with dilute base, washed with water, and dried and the ether pulled off under house vacuum. The products were isolated by vacuum distillation and by preparative gas chromatography on a Wilkens Autoprep, Model 700, using one or more of the columns listed in Table I. Analyses were run on a Varian Aerograph, Model 1200, gas chromatograph using one or more of the columns listed in Table I.

Diethyl 1-*p*-menthenyl 7-phosphonate (6) was prepared from 1 ($\alpha^{29}D$ −14.6°). Once initiated, this reaction was exothermic and heating had to be controlled to keep the reaction temperature below 150°. The yield was 32 g of crude **6** which glc analysis indicated was 80% (25.7 g) **6**, with an overall yield of 94%. An analytical sample was collected by pgc from a distillation cut (125–127° (0.1 mm)) of the crude product: d^{24} = 1.009, $n^{20}D$ 1.4649, $\alpha^{25}D$ −35.4°; ir 2910, 1430, 1385, 1360, 1245, 1160, 1095, 1045, 1025, 950, 845, 790 cm^{-1}; nmr δ 0.88 (d, 6, J = 6 Hz, $C_{9,10}$–CH_3), 1.25 (t, 6, J = 7 Hz, $C_{12,14}$–CH_3), 2.16 (d, 2, J = 22 Hz, C_7–CH_2), 4.02 (qn, 4, J = 7 Hz, $C_{11,13}$–CH_2), and 5.53 ppm (bs, 1, C_2-vinyl).

Anal. Calcd for $C_{14}H_{27}O_3P$: C, 61.29; H, 9.92; P, 11.29. Found: C, 61.11; H, 10.03; P, 11.48.

Compound **6** was prepared in the absence of peroxide by heating 0.1 mol (13.8 g) of 1 and 0.5 mol (69.1 g) of DEHP at 140–150° for 3.5 hr. The yield was 10.2 g of crude product which glc analysis indicated was 83% (8.5 g) **6** with an overall yield of 31%. Another run in which 0.05 mol (6.8 g) of 1 and 0.25 mol (34.5 g) of DEHP were heated at 75–85° for 3.5 hr yielded 6.2 g of crude product which glc indicated was 76% (4.7 g) **6** or an overall yield of 34%.

Diethyl 1-*p*-menthenyl-6-phosphonate (7) was prepared from 2 ($\alpha^{29}D$ +21.4°). The yield was 21 g of crude **7** which glc analysis indicated contained 73% (15.3 g) **7** with an overall yield of 56%. An analytical sample was collected by pgc from a distillation cut (106° (0.1 mm)) of the crude product: d^{24} = 1.008; $n^{20}D$ 1.4662; $\alpha^{25}D$ +53.1°; ir 2930, 1440, 1385, 1360, 1240, 1160, 1095, 1045, 1020, 950, 788 cm^{-1}; nmr δ 0.89 (d, 6, J = 6 Hz, $C_{9,10}$–CH_3), 1.29 (t, 6, J = Hz, $C_{12,14}$–CH_3), 1.83 (bs, 3, C_7–CH_3), 2.48 (dd, 1, J = 6, 22 Hz, C_6–CH) 4.06 (qn, 4, J = 7 Hz, $C_{11,13}$–CH_2), and 5.51 ppm (bs, 1, C_2-vinyl).

Anal. Calcd for $C_{14}H_{27}O_3P$: C, 61.29; H, 9.92; P, 11.29. Found: C, 61.13; H, 10.07; P, 11.16.

Compound **7** was prepared in the absence of the peroxide by heating 0.1 mol (18.6 g) of 2 and 0.5 mol (69.1 g) of DEHP at 140–150° for 3.75 hr. The yield was 9.2 g of crude **7** which glc analysis indicated was 72% of **7** with an overall yield of 24%.

Diethyl 10-*endo*- and -*exo*-isocamphanylphosphonates (8) were prepared from **3**. The yield was 25.5 g of crude product which glc analysis (12 ft × 3/16 in × 20% Carbowax 20M at 235° and He at 63 ml/min) indicated was 23% isomer 1, 73% isomer 2, and 4% unidentified. Isomers 1 and 2 were eluted at 14.4 and 15.4 min from the cyclohexane solvent peak. Isomer 1 was not isolated in high purity except for a few milligrams which were used for ir: isomer 1 ir 3400, 2900, 1460, 1385, 1360, 1240, 1155, 1080, 1050, 1020, 950, 856, 820, 800 cm^{-1}.

Diethyl 10-*endo*-isocamphanylphosphonate (8), isomer 2, was isolated by pgc (10 ft × 1/4 in. × 20% Carbowax 20M at 230° and He at 120 ml/min) in 90% purity: d^{24} = 1.0412; $n^{20}D$ 1.4704; ir, 3490, 2950, 1460, 1385, 1360, 1250, 1155, 1090, 1050, 1025, 955, 860, 792 cm^{-1}; nmr δ 0.81 (s, CH_3 cis to C_{10}) 0.98 (s, CH_3 trans to C_{10}), 1.32 (t, J = 7 Hz, $C_{12,14}$–CH_3), and 4.09 ppm (qn, J = 7 Hz, $C_{11,13}$–CH_2); for minor isomer 0.89 (s, CH_3 *cis* to C_{10}) and 1.05 ppm (s, CH_3 trans to C_{10}).

Anal. Calcd for $C_{14}H_{27}O_3P$: C, 61.29; H, 9.92; P, 11.29. Found: C, 61.09; H, 9.89; P, 11.45.

Isomers 1 and 2 were also prepared by heating 6.8 g (0.05 mol) of **4** and 34.5 g (0.25 mol) of DEHP at 140–150° for 3.5 hr. Work-up yielded 7.75 g of crude product which glc indicated was 23% isomer 1, 75% isomer 2, and 2% unidentified. This was a 55% crude yield.

Diethyl *p*-menthanyl-2-phosphonate (9) was prepared from **4** ($\alpha^{29}D$ +62.9°). The yield was 24.3 g of crude **9**. An analytical sample collected by pgc from a distillation cut (106–108° (0.2 mm)) of the crude product contained 7% **9a**, 77% **9b** and **c**, and 5% **9d**. It had d^{24} 1.0175, $n^{20}D$ 1.4578, $\alpha^{25}D$ +17.3°, nmr δ 0.88 (d, J = 5 Hz, $C_{9,10}$–CH_3), 1.12 (d, J = 6 Hz, C7–CH_3), 1.32 (t, J = 6 Hz, $C_{12,14}$–CH_3), and 4.10 (qn, J = 7 Hz, $C_{11,13}$–CH_2) ppm; ir 2910, 1450, 1385, 1360, 1240, 1200, 1160, 1095, 1055, 1030, 950, 782 cm^{-1}.

Anal. Calcd for $C_{14}H_{29}O_3P$: C, 60.84; H, 10.58; P, 11.41. Found: C, 61.01; H, 1070; P, 11.43.

Glc peaks **9a**, **b**, **c**, and **d** were isolated by repeated pgc collections from Carbowax 20M and then OV-17 columns. Isomer **9a** could not be isolated in better than 66% purity, with the major contaminant being **9b,c** (28%). Peak **9b,c** was isolated in 98% purity and **9d** in 94% purity: ir **9a** 3430, 2900, 1465, 1390, 1365, 1240, 1206, 1160, 1090, 1048, 1020, 945, 867, 788, 743, 698; **9b,c** 3430, 2910, 1465, 1390, 1365, 1235, 1200, 1155, 1090, 1050, 1025, 950, 782, 738; **9d** 3420, 2900, 1470, 1445, 1390, 1370, 1235, 1205, 1160, 1095, 1055, 1025, 950, 872, 784, 733, 697 cm^{-1}. See Table II for nmr data.

When heated at 140–150° for 3.5 hr, 6.9 g (0.05 mol) of **4** and 34.5 g (0.25 mol) of DEHP yielded only 0.96 g (7%) of crude **9**.

Reaction of DEHP with Limonene (5). A 34.5 g (0.25 mol) sample of DEHP was heated to 140° and 0.37 g (0.0025 mol) of DTBP added, then 6.8 g (0.05 mol) of **5** ($\alpha^{25}D$ +98.6°) was added dropwise over 0.5 hr, with heating and stirring continued for a total of 3.4 hr. Isolation of the product by diluting with water and extracting with ether yielded 13.1 g of crude product. Glc analysis (12 ft × 1/8 in. × 2% OV-17 at 250° and He at 32 ml/min) using methyl stearate as an internal standard, indicated that the product was 98% adduct (8.7% **10**, 32.2% **11**, 1.1% **12a**, 26.4% **12b**, 26.6% **12c**, and 2.9% **12d**). The response factor for **10** and **11** was 0.81× stearate and for **12a–d** was 0.39× stearate.

The isomers were concentrated by vacuum distillation through a spinning band column yielding a cut (98–102° (0.8 mm)) which contained 47% **10**, a trace of **11** and low-boiling materials, another cut (90–93° (0.5 mm)) containing 5% **10** and 91% **11**, and a cut (121–126° (0.1 mm)) containing 99% of the diadducts **12**. Isomers **10** and **11** were further purified by pgc (10 ft × 1/4 in. × 20 Carbowax 20M at 230° and He at 120 ml/min) to 95% purity.

In a similar run using 25.9 g (0.19 mol) of DEHP, 5.13 g (0.038 mol) of **5**, and 0.28 g (0.0019 mol) of DP and heating for 3.5 hr, then adding another 0.27 g of DTBP and continuing heating for 2.75 hr longer, the reaction was followed by sampling at intervals and analyzing by glc using the internal standard. The results are given in Table III.

Extractive isolation of the final product yielded 14.0 g of material (3.3% **10b**, 0.2% **11**, 2.0% **12a**, 40.5% **12b**, 44.2% **12c**, and 6.6%

12d). Allowing for sample withdrawal, the yield was 97.4% based on diphosphonate adduct.

Diethyl bornyl-2-phosphonate (10b): d^{24} = 1.0346, $n^{20}D$ 1.4692, $\alpha^{25}D$ 18.6°; ir 3450, 2910, 1455, 1385, 1365, 1285, 1235, 1155, 1090, 1055, 1025, 949, 787, 748 cm^{-1}; nmr δ 0.87 (s, 6, $C_{8,9}$-CH_3), 1.02 (s, 3, C_{10}-CH_3), 1.32 (t, 6, J = 7 Hz, $C_{12,14}$-CH_3), and 4.12 ppm (qn, 4, J = 7 Hz, $C_{11,13}$-CH_2).

Anal. Calcd for $C_{14}H_{27}O_3P$: C, 61.29, H, 9.92; P, 11.29. Found: C, 61.09; H, 10.11; P, 11.44.

Diethyl 1-*p*-menthenyl-9-phosphonate (11): d^{24} = 1.0076, $n^{20}D$ 1.4680, $\alpha^{26}D$ +11.7°; ir 3415, 2880, 1430, 1380, 1235, 1155, 1090, 1050, 1025, 952, 875, 829, 792, 714 cm^{-1}; nmr δ 1.03 (d, 3, J = 6.5 Hz, C_{10}-CH_3), 1.32 (t, 6, J = 7 Hz, $C_{12,14}$-CH_3), 1.64 (s, 3, C_7-CH_3), 4.09 (qn, 4, J = 7 Hz, $C_{11,13}$-CH_2).

Anal. Calcd for $C_{14}H_{27}O_3P$: C, 61.29; H, 9.92; P, 11.29. Found: C, 61.43; H, 10.00; P, 11.17.

Diethyl *p*-methanyl-2,9-diphosphonate (12): glc 2.5% **12a**, 45.5% **12b**, 45.9% **12c**, 6% **12d**; d^{24} = 1.0894, $n^{25}D$ 1.4676, $\alpha^{25}D$ +4.9°; ir 3440, 2890, 1430, 1380, 1230, 1155, 1090, 1045, 1020, 942, 823, 784 cm^{-1}; nmr δ 1.04 (d, 6, J = 6 Hz, $C_{7,10}$-CH_3), 1.34 (t, 12, J = 7 Hz, $C_{12,14,16,18}$-CH_3), 4.11 ppm (qn, 8, J = 7 Hz, $C_{11,13,15,17}$-CH_2).

Anal. Calcd for $C_{18}H_{38}O_6P_2$: C, 52.41; H, 9.29; P, 15.02. Found: C, 52.23; H, 9.41; P, 14.96.

When heated at 140–150° for 3.5 hr, 13.6 g of 5 and 60.1 g of DEHP yielded 3.04 g (11.1%) of crude product which had a composition similar to the run with the peroxide.

Hydrogenation of the Limonene Adducts. A 0.3 g sample of **10** was reduced in 10 ml of acetic acid using 29.5 mg of PtO_2 as catalyst. The sample absorbed only 2.45 ml (STP 13% of theory) of H_2 in 42 min. Glc of the 0.29 g recovered indicated that it was mostly starting material.

A 0.16 g sample of 11 and 26.2 $MgPtO_2$ in 5 ml of acetic acid absorbed 12.84 ml (STP, 98% of theory) of H_2 in 44 min. Glc of the recovered material (0.15 g, $[\alpha]^{25}D$ 0° (15% EtOH)) showed a peak at α (11) 0.731. Ir bands at 1250–970 cm^{-1} indicated the presence of the phosphonate structure.

Acknowledgments. The authors wish to thank Mr. G. Boudreaux, Southern Regional Research Center, New Orleans, La., and Mr. R. C. Rosanski, Florida State University, Tallahassee, Fla., for determining the nmr spectra.

Registry No.—**1**, 18172-67-3; **2**, 7785-70-8; **3**, 79-92-5; **4**, 1195-31-9; **5**, 5989-27-5; **6**, 49830-14-0; **7**, 49830-15-1; *endo*-**8**, 49830-16-2; *exo*-**8**, 49830-17-3; **9a**, 49775-19-1; **9b**, 49775-20-4; **9c**, 49775-21-5; **9d**, 49775-22-6; **10b**, 49830-18-4; **11**, 49830-19-5; **12**, 49830-20-8.

References and Notes

(1) (a) Address correspondence to this author at the Southern Regional Center, New Orleans, La. 70179. (b) One of the Laboratories of the Southern Region, Agricultural Research Service, U. S. Department of Agriculture.
(2) A. N. Pudovik and I. W. Konovalona, *Zh. Obsch. Khim.*, **29**, 3342 (1959); *Chem. Abstr.*, **54**, 15224*b* (1960).
(3) A. R. Stiles, W. E. Vaughan, and F. F. Rust, *J. Amer. Chem. Soc.*, **80**, 714 (1958).
(4) J. J. Callot and C. Benezra, *Can. J. Chem.*, **49**, 500 (1971).
(5) D. E. Oldroyd, G. S. Fisher, and L. A. Goldblatt, *J. Amer. Chem. Soc.*, **72**, 2407 (1950).
(6) J. B. Strothers, *Tech. Org. Chem.*, **11**, 199 (1963).
(7) D. J. Trecker and J. P. Henry, *J. Amer. Chem. Soc.*, **85**, 3204 (1963).
(8) M_D = *ca.* +280° after allowance for the low optical purity of **2**. The corresponding alcohol, *trans*-carvotanacetol, has $M_D \sim 252°$ [E. E. Royals and J. C. Leffingwell, *J. Org. Chem.*, **31**, 1937 (1966)].
(9) D. I. Davis, L. J. Parfitt, C. Kalden and J. A. Claisse, *J. Chem. Soc. C*, 1585 (1969).
(10) Data on 2,2-dimethylnorbornane are not available, but in 3-methylene derivatives the two methyls have the same chemical shift [A. T. Blomquist, R. J. Himics, and J. D. Meador, *J. Org. Chem.*, **33**, 2462 (1968)]. Hence, the observed differences are due to the cis-trans relationship to C_{10}. In the absence of data on analogous norbornanes, the high field signals were assigned to the cis methyls by analogy to methylcyclopentanes and 3,3-dimethylcyclopentenes. Methyls trans to a vicinal substituent experience very slight shielding [$\lesssim$0.05 ppm, M. Christl, H. J. Reich, and J. D. Roberts, *J. Amer. Chem. Soc.*, **93**, 3463 (1971)]. The methyls of 1,1-dimethylcyclopentane have δ 0.98 ppm. We have observed (unpublished results) shifts of 0.90 and 0.52 ppm for the geminal methyls of *cis*-1-(2-acetoxyethyl)-2,2,3-trimethylcyclopentane, indicating *ca.* 0.5 ppm shielding by the two cis substituents. An 0.18 ppm shielding of one of the methyls of 4-(2-acetoxyethyl)-2,3,3-trimethylcyclopentene relative to those of the 1-(2-acetoxyethyl) isomer confirmed the strong shielding effect of a cis vicinal CH_2X group on a cyclopentyl methyl, even when X is a deshielding group.
(11) N. A. LeBel, R. F. Czaja, and A. De Boer, *J. Org. Chem.*, **34**, 3112 (1969).
(12) No further work was done on this peak. It is assumed to be 1-*trans*-*p*-menthanyl phosphonate.
(13) Difficulty in separating this peak from the first minor isomer made it impractical to get a representative sample or to get enough of the first minor peak of nmr.
(14) Y.-R. Naves, *Helv. Chem. Acta*, **47**, 1617 (1964).
(15) S. H. Schroeter and E. E. Eliel, *J. Org. Chem.*, **30**, 1 (1965).
(16) This is in accord with J. H. Brewster's rules [*J. Amer. Chem. Soc.*, **81**, 5483 (1959)], which predict the same interrelationship for the isomeric phosphonates.
(17) Even with the OH group at least half has this conformation.[14,15]
(18) P. S. Skell and R. C. Woodward, *J. Amer. Chem. Soc.*, **77**, 4638 (1955).
(19) A. J. Birch, *Ann. Rep. Progr. Chem.*, **47**, 177 (1950).
(20) The carvomethene was kindly supplied by Newport Industries, the α-pinene by Arizona Chemical Co., the β-pinene by Crosby Chemicals, Inc., and the diethyl hydrogen phosphite by Mobil Chemical. Use of a company and/or product name by the department is for the convenience of the reader and does not imply approval or recommendation of the product to the exclusion of others which may also be suitable.

Some Properties and Reactions of 1-Methyl-3-phospholanone 1-Oxide[1]

Louis D. Quin* and Ronald C. Stocks

Gross Chemical Laboratory, Department of Chemistry, Duke University, Durham, North Carolina 27706

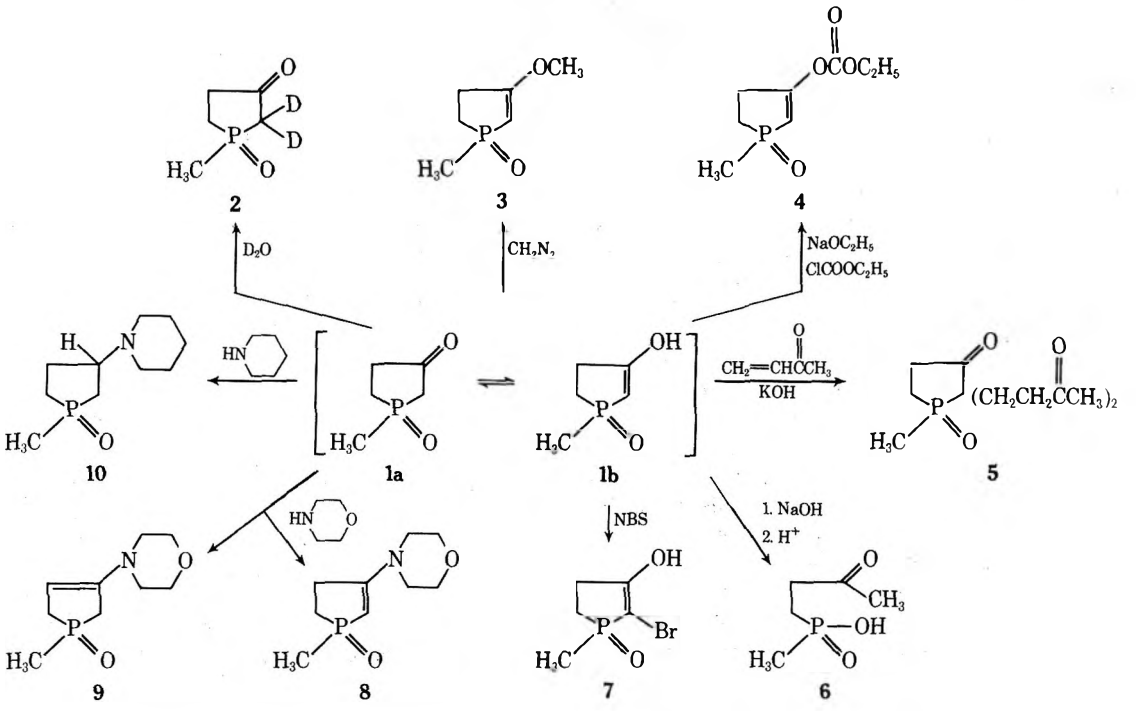
Received September 21, 1973

1-Methyl-3-phospholanone 1-oxide (1) is in tautomeric equilibrium with 1-methyl-3-hydroxy-2-phospholene 1-oxide, permitting uncatalyzed rapid exchange with D_2O at the 2 position. In appropriate media, the ^{13}C nmr spectra of both keto and enol forms can be observed, giving conclusive assignment of the enol structure. Reactions of 1 can occur at oxygen (with diazomethane or ethyl chloroformate), at C-2 (with *N*-bromosuccinimide or Michael addition to 2-butenone), at C-3 (enamine formation), or at phosphorus (ring opening with base). Some of the functionally substituted phosphine oxides so obtained were reduced to the phosphines with trichlorosilane. Of particular importance was the reduction of 1 itself which gave 1-methyl-3-phospholanone, the first known ketophospholane.

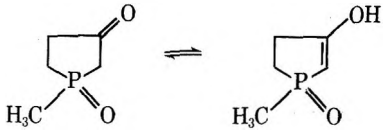
In 1968,[2] we reported the synthesis of the first keto derivative of the phospholane oxide system,[3] 1-methyl-3-phospholanone oxide (1). The compound was found to have considerable enolic character; depending on the medium, as much as 20–25% could be present as the enol **1b**. Conditions favoring the enol form were those where intermolecular hydrogen bonding was enhanced (high concentrations in aprotic solvents, or the solid state). The tautomeric forms were easily recognizable in admixture by substantial differences in their ir and nmr (^1H and ^{31}P) spectra.

In the present paper, we report further on the tautomeric character of this compound, particularly as it influences other properties. The compound has been demonstrated to

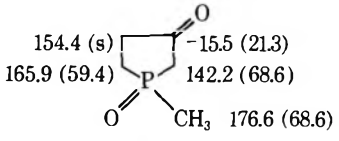
Scheme I



have utility as a precursor of a variety of functionally substituted phospholane derivatives.



Carbon-13 Nmr Spectra. The spectrum of a dilute chloroform solution of compound 1 was clearly that of the keto form (**1a**). The carbonyl group absorbed at δ −15.5, which is in its characteristic region, and no olefinic carbon signals were present. Other assignments are shown below; δ values are relative to CS_2 = 0, and J_{PC} values are in parentheses.



The large coupling of P with adjacent C in cyclic phosphine oxides[4,5] was helpful in assigning these carbons; the deshielding effect of C=O[6a] allowed ready recognition of the carbon α to it and to P=O. Upon increasing the concentration of the solution, additional signals due to the enol form appeared. Those at δ 16.6 (45) and 102.1 (115) are assignable to olefinic carbons, the former being that bearing hydroxy.[7] Similar wide differences, explainable by resonance, are also known among enol ethers[6b] and indeed are seen in 1-methyl-3-methoxy-2-phospholene[8] (**11**, δ 23.6 and 100.1).

The ^{13}C studies provide unequivocal proof that the enol does indeed have the double bond in the 2,3 position, as postulated previously,[2] and not in the 3,4 position.

In water solution, only the keto form was detected, regardless of concentration. This would suggest that water is competing with the enolic OH in forming a hydrogen bond to phosphoryl, thus eliminating this source of stabilization of the enol. That hydrogen bonding by water is present is clearly revealed by the significant differences between the ^{13}C values for **1a** in $CHCl_3$ and in water (CH_3, δ 172.1; C-2, 145.5; C=O, −6.7; C-4, 148.6; C-5, 160.1).

The tautomeric equilibrium provides a vehicle for rapid exchange of the protons at C-2 with deuterium. Dideuterio derivative **2** was obtained simply on several exposures of **1** to fresh D_2O, in the absence of base. The location of the deuterium was revealed by the ^{13}C spectrum in D_2O solution; the doublet for C-2, seen at δ 145.5 in H_2O, was virtually eliminated, while no other changes occurred. Such simplification of ^{13}C spectra by exchanging H for D has been reported elsewhere,[10] and is a consequence of the splitting of the carbon signal by the (undecoupled) deuterium, and of the weakening of the signal relative to the other carbons by the diminished nuclear Overhauser effect. In our case, the signal simply vanished into the base line.

Reactions at the Keto-Enol Site. Reactions of compound **1** that gave definite products are shown in Scheme I. It is seen that products can be derived from attack on oxygen, C-2, or C-3. Enol ether **3** was formed with diazomethane, while enol carbonate **4** was formed with ethyl chloroformate. The latter reaction, conducted on the enolate ion, could have been accompanied by C-acylation, but none was observed. Indeed, in only one of several other attempts to effect attack at C-2 was the desired result obtained; twofold Michael addition of the enolate to methyl vinyl ketone occurred in dilute aqueous base to form a product lacking the enolic properties of the 3-phospholanone oxide system yet showing ir absorption for a ring carbonyl (1725 cm^{-1}; exocyclic $\nu_{C=O}$ occurred at 1710 cm^{-1}). The structure proposed is **5**, and this was supported by the presence of a 6 H singlet for the two CH_3CO groups.

In some other attempts to effect condensations in aqueous base, a product was obtained that appeared to be noncyclic. An intentional attempt to effect ring opening of **1** with hot sodium hydroxide proved successful, and a compound identified as methyl(3-oxobutyl)phosphinic acid (**6**) was obtained in high yield. This sensitivity of the keto phosphine oxide to base parallels that known also in cyclic β-diketones.[11]

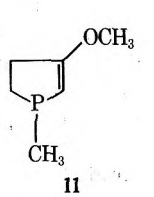
Oxide **1** absorbed 2 mol of bromine in water–methanol at titration rate. Since the oxide is spectroscopically seen as the keto form **1a** in this medium, the conversion of keto to the reactive enol form must be very rapid. Attempts to

isolate a product gave only oils. However, a crystalline monobromo derivative (7) was obtained in 38% yield with *N*-bromosuccinimide in hot chloroform, a procedure useful for the bromination of cyclic β-diketones.[12] This bromo compound was seen from its ir spectrum to be entirely in the enol form; no C=O absorption was present. Location of the bromine at the 2 position, as expected from the β-diketone reaction,[12] was suggested from titration with bromine, since only 1 mol was consumed. The compound had low solubility in organic solvents and attempts at performing some typical α-halo ketone reactions so far have been unsuccessful.

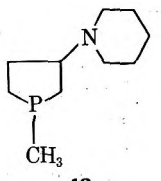
Another typical carbonyl reaction given by **1** is enamine formation with morpholine. The product was a mixture of two position isomers, **8** (85%) and **9** (15%). The predominance of the oxide with the 2-phospholene ring is consistent with other observations of greater stability for this ring system than for the 3-phospholene system,[13] and is suggestive of some stabilization of the double bond by conjugation with the phosphoryl group. Another indication of some interaction between these groups was the lack of reactivity of the 2 position to alkylating or acylating reagents. Normally, this carbon is a reactive site in enamines, and such reactions occur with ease. However, conjugation with a carbonyl group is known to deactivate this position, and enamino ketones undergo alkylation on oxygen.[14] Acylic phosphorylenamines have recently become available,[15] but so far no information has been published on the reactivity of the corresponding enamine carbon in these compounds.

When piperidine was used for enamine formation, the major product was a saturated amine (**10**), formed by reduction of initially formed 1-methyl-3-piperidino-2-phospholene 1-oxide. Such reduced products have been obtained by others when excess piperidine is used, but in the presence of added acid.[16] The present result would suggest that the enolic character of **1** provides sufficient acidity for the reaction to proceed.

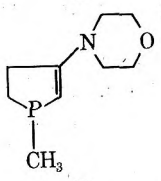
Reduction of the Phosphine Oxide Function. Several years ago, silanes were introduced as reagents for reducing phosphine oxides to phosphines,[17] and the method has since found wide use. Some of the oxides prepared in the present study were unique in containing functional groups, and offered the possibility of serving as precursors to the corresponding phosphines. We have found that these oxides react with trichlorosilane in a normal manner, and functionally substituted phosphines **11**, **12**, and a mixture of **13** (85%) and **14** (15%) were prepared. Phospholenes **11** and **13** were of special interest spectroscopically, as they provided further examples of exceptionally large coupling of phosphorus with the 2 proton[18] (38 and 40 Hz, respectively). The ^{31}P nmr shifts for these vinyl phosphines were similar (+14.4 and +18.1 ppm, respectively) and like that of 1,3-dimethyl-3-phospholene (+15.2[18]), indicating little transmission through the double bond of the electronic character of the substituent.



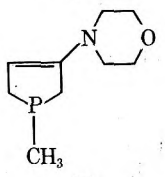
11



12

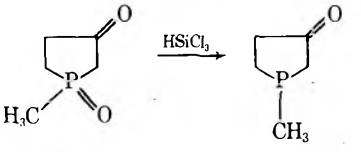


13



14

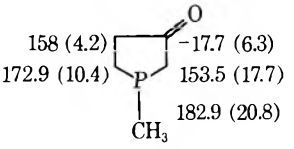
Synthesis of 1-Methyl-3-phospholanone. By applying the trichlorosilane reduction directly to phosphine oxide **1**, we have prepared the first keto derivative (**15**) in the phospholane series. No interference by the carbonyl group[19] was evident in this reaction. While the yield was only 21%, the product was obtained in good purity. This ketone does not show the tendency to exist in the enol form as exhibited by the phosphoryl derivative (**1**).



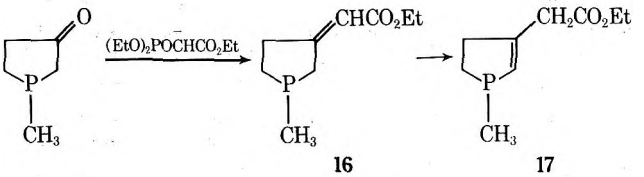
15

Attempts to prepare ketone **15** by acid hydrolysis of enol ether **11** or enamine **13** were not very successful. These compounds showed unusual reluctance to undergo hydrolysis. In the acid medium, they probably would exist in phosphonium salt form, which would impede the further protonation required for carbonyl formation.

Ketone **15** was easily characterized by its spectral properties. Its ^{13}C spectrum (in $CHCl_3$), compared with that of **1a**, exemplifies quite well the considerable differences in J_{PC} between a phosphine and its oxides, and at the same time the similarity in chemical shifts. As for **1a**, carbons α to phosphorus have the larger coupling constant, and the deshielding effect of C=O assists in locating C-2.



Availability of ketone **15** prompted examination of an anomalous property observed for a derivative of the homologous ketone 1-methyl-4-phosphorinanone. The carbethoxymethylene derivative of the latter was found to be prone to rearrange to the endocyclic olefinic structure.[20] When **15** was subjected to the Wadsworth-Emmons olefination to produce ester **16**, the product was found to consist chiefly (60–65%) of the rearranged form (**17**). The 2-phospholene structure was easily recognized from the characteristically large (41 Hz) coupling of the olefinic proton with phosphorus. Even greater propensity for rearrangement is therefore present in this ring system; the six-membered ring required base catalysis for rearrangement to the endocyclic structure.



16 17

Experimental Section

General. Melting points were taken on a Mel-Temp apparatus and are corrected; boiling points are uncorrected. Proton nmr spectra were taken on a Varian A-60 spectrometer; chemical shifts are relative to external TMS. Phosphorus nmr spectra were obtained with a Varian V-4300B spectrometer at 19.3 MHz or a Bruker HFX-10 system at 36.43 MHz, and are referenced to 85% H_3PO_4. Proton noise-decoupled Fourier transform ^{13}C spectra were obtained on the Bruker system at 22.62 MHz utilizing C_6H_6 in a 3-mm coaxial capillary as an external heteronuclear lock; chemical shifts are referenced to CS_2. Gas chromatography (gc) was performed with a Varian Aerograph 202-B chromatograph on a 150-cm column of OV-17 (4%) on Chromosorb G at 60 ml/min

of helium. Chloroprene (50% in xylene) was generously provided by the Du Pont Co. Analyses were performed by the Galbraith (Knoxville, Tenn.) or Schwarzkopf (Woodside, N. Y.) Laboratories. All reactions or transfers of phosphines were conducted in a nitrogen atmosphere in a glove bag.

1-Methyl-3-phospholanone 1-Oxide (1). A mixture of $\Delta^{2,3}$ (90%) and $\Delta^{3,4}$ (10%) 1-methyl-3-chlorophospholene oxides was obtained[2] by slow addition of the chloroprene–methylphosphonous dichloride adduct[21] to ice water. After 12 hr, the mixture was neutralized with K_2CO_3. The solution was extracted continuously with chloroform; from the extract was obtained a colorless oil which solidified on standing, mp 58–62°, bp 87–90° (0.1 mm).

A solution of 85.3 g (0.586 mol) of the above oxide in 100 ml of methanol was added to 400 ml of methanol treated previously with 13.5 g (0.586 mol) of sodium. The mixture was stirred at room temperature for 1 hr and then refluxed for 6 hr, during which time sodium chloride precipitated. After being cooled, the mixture was acidified with 6 *N* HCl and then stripped to dryness. Extraction of the residue with benzene provided crude 1-methyl-3-methoxy-2-phospholene oxide[2] (**3**). Distillation of a small sample gave bp 116–120° (0.15 mm), correcting a value [90° (0.15 mm)] previously reported.[2] The ir and nmr properties agreed with those already published.[2]

Anal. Calcd for $C_6H_{11}O_2P$: C, 49.31; H, 7.59; P, 21.20. Found: C, 49.17; H, 7.47; P, 21.38.

The crude **3** was placed in a solution of 100 ml of water and 1 ml of 6 *N* HCl. The solution was heated on a steam bath for 6 hr and then extracted with two 50-ml portions of methylene chloride. The aqueous layer was further extracted continuously with methylene chloride for 3 days. The combined extracts were dried ($MgSO_4$) and then concentrated on a rotary evaporator. The residue was taken up in a minimal amount of hot benzene and placed in the refrigerator. After a few days, the white solid that had precipitated (39% from the mixed chlorophospholene oxides) was removed by filtration. Recrystallization from benzene gave a solid: mp 89–91°; nmr (concentrated $CDCl_3$ solution) δ 2.12 (doublet, $^2J_{PH}$ = 13.2 Hz, PCH_3), 2.27 (doublet, $^2J_{PH}$ = 13.5 Hz, PCH_3), 2.51–3.63 (complex, $-CH_2-$), 5.41 (doublet, $^2J_{PCH}$ = 20.5 Hz, C=CH) (on dilution of the sample, the doublets at δ 2.12 and 5.41 due to **1b** disappeared): ir spectrum ($CHCl_3$, concentrated) 3450 (–OH), 1740 (C=O), 1590 cm^{-1} (C=C) (dilution of the sample significantly decreased the **1b** peaks at 3450 and 1590 cm^{-1}); ^{31}P nmr ($CHCl_3$, concentrated) δ −51.0 (**1a**) and −60.5 (**1b**).

Anal. Calcd for $C_5H_9O_2P$: C, 45.46; H, 6.87; P, 23.45. Found: C, 45.50; H, 7.03; P, 23.47.

The 2,4-dinitrophenylhydrazone, recrystallized from methanol, had mp 207–207.5°.

Anal. Calcd for $C_{11}H_{13}N_4O_5P$: C, 42.31; H, 4.20; N, 17.95; P, 9.92. Found: C, 42.51; H, 4.50; N, 18.05; P, 9.64.

A solution of 0.175 g (1.33 mmol) of **1** in 10 ml of water–methanol (1:1) was titrated with bromine. A total of 0.15 ml (0.44 g, 2.7 mmol) of bromine was decolorized at a titratable rate. The addition of one additional drop gave a deep bromine color which persisted for several minutes.

Deuteration of **1** was accomplished by allowing a solution of 1.0 g in 5 ml of D_2O to stand for 30 min and then removing the solvent by a rotary evaporator *in vacuo*. This procedure was repeated three times. The residual solid was recrystallized from benzene to give **2**. Integration of the ^1H nmr spectrum showed that 2 H had been eliminated from the 6 H complex methylene region of **1a**.

The ^{13}C nmr spectra of **1** and **2** are reported in the discussion.

1-Methyl-3-methoxy-2-phospholene 1-Oxide (3) from 1 and Diazomethane. A mixture of 5.0 g (0.038 mol) of phospholanone **1** in 300 ml of benzene containing 1 ml of boron trifluoride etherate was treated with excess diazomethane. After standing overnight, the solution was freed of a small amount of solid by decantation and then concentrated *in vacuo* to a small volume. On pouring into ether, there was precipitated 2.4 g of unreacted **1**. From this filtrate was recovered 0.7 g (13%) of enol ether **3**, identified by comparison of its nmr spectrum with that of a known sample.[2]

1-Methyl-3-methoxy-2-phospholene (11). A solution of 4.6 g (32 mmol) of 1-methyl-3-methoxy-2-phospholene oxide (**3**) in 200 ml of benzene was freed of traces of water by distilling off some of the benzene. While at 0°, the solution was treated with 3.24 g (32.1 mmol) of triethylamine and then over 30 min with 4.13 g (31.5 mmol) of trichlorosilane in 30 ml of benzene. The mixture was then refluxed for 2 hr. Hydrolysis with 10 *N* NaOH was performed slowly with ice-bath cooling, giving a clear solution. The benzene layer was removed, and the aqueous layer was extracted with 100 ml of benzene. After drying ($MgSO_4$), distillation was performed to give 1.82 g (45.2%): bp 63.5–65° (16 mm); nmr ($CDCl_3$) δ 1.45 (doublet, $^2J_{PH}$ = 3.0 Hz, PCH_3), 1.60–3.80 (complex signals), 4.01 (s, OCH_3), 5.04 (doublet, $^2J_{PH}$ = 38 Hz, C=CH); ^{31}P nmr ($CDCl_3$) +14.4; ir (neat) $\nu_{C=C}$ 1585 cm^{-1}. The compound was analyzed as the benzyl bromide salt, recrystallized from methanol–ethyl acetate, mp 181–182°.

Anal. Calcd for $C_{13}H_{18}BrOP$: C, 51.82; H, 6.03; P, 10.29. Found: C, 52.18; H, 6.10; P, 10.77.

Reaction of 1-Methyl-3-phospholanone 1-Oxide with Ethyl Chloroformate. A mixture of 30 ml of dimethylformamide, 1.0 g (7.6 mmol) of **1**, and 0.43 g (8.0 mmol) of sodium methoxide was stirred at room temperature for 10 hr, during which time a tan solid formed. The solid was removed by filtration, placed in a small flask, and treated directly with ethyl chloroformate (15 ml) in one portion. After overnight stirring, water (30 ml) was added to the mixture and stirring was continued for 1 hr. The acid solution was neutralized with sodium carbonate and then continuously extracted with chloroform overnight. The extract was dried ($MgSO_4$) and concentrated on a rotary evaporator to give a yellow oil. The product (**4**) had nmr (neat) δ 2.04 (doublet, $^2J_{PH}$ = 13 Hz, PCH_3), 6.50 (doublet of triplets, $^2J_{PH}$ = 18 Hz, $J_{allylic}$ = 1.5 Hz, =CH); ir (neat) 1770 cm^{-1} (C=O of enol ester). Attempts to purify the oil by distillation failed owing to decomposition.

1-Methyl-2,2-bis(3-oxobutyl)phospholan-3-one Oxide (5). A mixture of 1.0 g (7.58 mmol) of **1**, 30 ml of water, 5 ml of 95% ethanol, 0.86 g (12.3 mmol) of 2-butenone, and a drop of concentrated potassium hydroxide was stirred at room temperature for 4 hr and then refluxed for 4 hr. It was then cooled, acidified with dilute hydrochloric acid, and extracted with methylene chloride overnight. The methylene chloride extract was dried ($MgSO_4$) and then concentrated on a rotary evaporator to give a yellow oil. Addition of warm benzene to the residue precipitated 0.74 g (36%) of a white solid which was removed by filtration: nmr (D_2O) δ 1.85 (singlet, 2 H), 2.06 (doublet, $^2J_{PH}$ = 12.5 Hz, PCH_3, 3 H), 2.25–3.50 (complex, $-CH_2-$), 2.70 (singlet, CH_3CO, 6 H); ir (Nujol) 1725 (ring C=O), 1710 cm^{-1} (chain C=O). A sample recrystallized from methanol–ether had mp 210–211.5°. The sample failed to decolorize bromine.

Anal. Calcd for $C_{13}H_{21}O_4P$: C, 57.32; H, 7.79; P, 11.38. Found: C, 57.36; H, 7.86; P, 11.50.

Methyl(3-oxobutyl)phosphinic Acid (6). A solution of 4.0 g (30.3 mmol) of **1** in 50 ml of 2 *N* sodium hydroxide solution was refluxed overnight and then acidified with concentrated hydrochloric acid. The solution was evaporated to dryness on a rotary evaporator. Methanol (50 ml) was added to the solid residue and after 15 min of stirring a precipitate of NaCl was filtered off. The filtrate was evaporated to dryness on a rotary evaporator to give 3.82 g (84%) of **6**, a tan solid of indefinite melting point (with decomposition): nmr (D_2O) δ 1.74 (doublet, $^2J_{PH}$ = 13.5 Hz, PCH_3), 1.95–2.54 (complex, β CH_2-), 2.74 (singlet, $COCH_3$), 3.03–3.52 (complex, α CH_2-); ir (Nujol) 3230 and 2192 (OH), 1705 (C=O), ~1660 (OH, dimer), 1040 cm^{-1} (POH). The compound in water formed a bright orange precipitate of a 2,4-dinitrophenylhydrazone, which when recrystallized from ethanol had mp 204.5–206.5°.

Anal. Calcd for $C_{11}H_{15}N_4O_6P$: P, 9.38. Found: P, 9.32.

1-Methyl-2-bromo-3-phospholanone 1-Oxide (7). To 150 ml of chloroform was added 10.0 g (75.8 mmol) of **1** and 13.5 (75.8 mmol) of recrystallized *N*-bromosuccinimide. The mixture was stirred until homogeneous and then refluxed for 18 hr. A tan precipitate formed. The mixture was cooled and the solid (**7**) was removed by filtration. After washing with chloroform, there was obtained 6.07 g (38%): mp 153–154°; nmr (DMSO-d_6) δ 1.89 (doublet, $^2J_{PH}$ = 13.5 Hz, PCH_3), 2.10–3.32 (complex, $-CH_2-$), 3.70 (multiplet); ir (Nujol) 1637 cm^{-1} (C=C) with no $\nu_{C=O}$ signal

Anal. Calcd for $C_5H_8BrO_2P$: C, 28.46, H, 3.82; Br, 37.87; P, 14.66. Found: C, 28.23; H, 3.88; Br, 38.06; P, 14.69.

A sample of **7** (0.24 g, 1.14 mmol) dissolved in methanol–water (1:1) decolorized bromine at a titratable rate until 0.06 ml (0.18 g, 1.1 mmol) was added. The addition of one additional drop (0.01 ml) gave a deep bromine color which persisted for several minutes.

1-Methyl-3-piperidinophospholane (12) and Its Oxide (10). A solution of 2.0 g (17 mmol) of phospholanone oxide **1**, 3 ml of piperidine, and 100 ml of benzene was refluxed for 12 hr in a Dean-Stark apparatus to permit water removal. Solvent and excess piperidine were then removed and the residue of **10** was taken up in 200 ml of fresh benzene for reduction with trichlorosilane–triethylamine. The same procedure as for the preparation of **11** was fol-

lowed, except that the acidic solution from the hydrolysis was stirred for 20 hr before basification. This removed some (about 20%) enamine which accompanied the main product (**12**). Distillation gave 0.71 g (25.6%) of **12**: bp 71–71.5° (0.45 mm); nmr ($CDCl_3$) δ 1.55 (doublet, $^2J_{PH}$ = 3 Hz, PCH_3), 1.65–3.50 (complex absorption for ring protons); no absorption for olefinic protons was present, nor was $\nu_{C=O}$ observed in the ir spectrum; ^{31}P ($CDCl_3$) δ +39.2.

Anal. Calcd for $C_{10}H_{29}NP$: C, 64.82; H, 10.89; P, 16.73. Found: C, 64.92; H, 10.91; P, 16.65.

Formation and Reduction of Mixed Enamines from 1-Methyl-3-phospholanone 1-Oxide and Morpholine. A solution of 4.0 g (30.3 mmol) of **1** and 5 ml of morpholine in 200 ml of benzene was refluxed on a Dean-Stark apparatus overnight. Benzene was then distilled to leave about 20 ml of solution, and the remaining solvent was removed *in vacuo*. The residue was a yellow solid whose nmr spectrum (benzene) showed that **1** had been transformed to the enamine **8**: δ 1.27 (doublet, $^2J_{PH}$ = 13 Hz, PCH_3), 1.46–2.12 (complex multiplet, $-CH_2-$), 2.44 and 3.19 (unsymmetrical triplets, morpholine $-CH_2-$), 4.36 (doublet, J_{PCH} = 18.5 Hz,C=CH). The product also contained some of the $\Delta^{3,4}$ isomer (**9**), and was used directly in other studies.

Attempts to alkylate (methyl iodide or benzyl chloride) and acylate (benzoyl or acetyl chlorides, or ethyl chloroformate) were unsuccessful, resulting after hydrolysis in recovery of the original ketone **1**.

The enamine mixture from above was dissolved in 150 ml of benzene and reduced with trichlorosilane–triethylamine as in the preparation of **11**. Distillation of the product gave 3.58 g (64%) at 101–106° (1.05 mm), whose nmr spectrum (benzene) revealed that an isomer mixture was present. The major component (83.8%) was determined to be 1-methyl-3-morpholino-2-phospholene (**13**):[22] nmr δ 1.20 (doublet, $^2J_{PH}$ = 2.5 Hz, PCH_3), 4.71 (doublet, $^2J_{PH}$ = 40 Hz, C=CH); ^{31}P δ +18.1; ir (neat) $\nu_{C=C}$ 1565 cm^{-1}. The other component (16.2%) was the $\Delta^{3,4}$ isomer (**14**): nmr δ 1.18 (doublet, $^2J_{PH}$ = 3 Hz, PCH_3), 4.75 (doublet, $^3J_{PH}$ = 7.5 Hz, C=CH); ir $\nu_{C=C}$ 1630 cm^{-1}. Separation of the mixture was not performed.

1-Methyl-3-phospholanone (15). Using the previously described (for **11**) method, ketone **1** (4.0 g, 30 mmol) was reduced with 2 molar equiv of trichlorosilane–triethylamine to give 0.73 g (20.8%) of **15**: bp 73–74° (17 mm); nmr (benzene) δ 0.69 (doublet, $^2J_{PH}$ = 3.2 Hz, PCH_3), 0.99–2.48 (multiplet, ring CH_2); ^{31}P nmr (benzene) δ +45.7; ir (neat) $\nu_{C=O}$ 1720 cm^{-1}. The benzyl bromide salt, recrystallized from methanol–ethyl acetate, had mp 170.5–171.5°.

Anal. Calcd for $C_{12}H_{26}BrOP$: C, 50.17; H, 5.62; P, 10.79. Found: C, 49.93; H, 5.55; P, 10.77.

Reaction of 1-Methyl-3-phospholanone with Triethyl Phosphonoacetate. A slurry of 0.238 g (0.993 mmol) of sodium hydride in 50 ml of dimethoxyethane (DME) was treated with a solution of 2.22 g (0.993 mmol) of triethyl phosphonoacetate in 10 ml of DME over a period of 10 min. After 30 min of stirring, a solution of 1.15 g (0.993 mmol) of 1-methyl-3-phospholanone (**15**) in 10 ml of DME was added over a 30-min period. The mixture was stirred at room temperature for 20 hr. The liquid was then decanted from a viscous deposit on the walls of the flask into 150 ml of benzene. The mixture was extracted with three 70-ml portions of benzene. The extract was dried ($MgSO_4$) and distilled; product was collected at 78–131° (18 mm). Redistillation gave some **15** and a major fraction at 124–131° (18 mm). Gc revealed this fraction to be a mixture with the major component (62.8%) being the 2-phospholene derivative (**17**), as indicated from the nmr spectrum of the mixture (olefinic signal at δ 6.17, J_{PCH} = 41 Hz). Another component (28.8%) appeared to be the unrearranged product **16** from the nmr spectrum, which contained another olefinic signal (δ 6.16, broad s) in the proper ratio to **17**. The third component (8.4%) was not identified.

Registry No. **1**, 21229-61-8; **1** 2,4-dinitrophenylhydrazone, 49849-22-1; **2**, 49849-23-2; **3**, 21229-62-9; **4**, 49849-24-3; **5**, 49849-25-4; **6**, 49849-26-5; **6** 2,4-dinitrophenylhydrazone, 49849-27-6; **7**, 50599-76-3; **12**, 49849-32-3; **13**, 49849-33-4; **14**, 49849-34-5; **15**, 49849-35-6; **15** benzyl bromide salt, 50599-77-4; **17**, 49849-37-8; chloroprene–methylphosphonous dichloride, 49849-38-9.

References and Notes

(1) Taken in part from the Ph.D. Dissertation of R. C. Stocks, Duke University, 1973. Supported by Public Health Service Grant CA-05507 from the National Cancer Institute. The Bruker spectrometer was purchased in part with funds provided by the National Science Foundation, Grant No. GP-10301.
(2) L. D. Quin and J. A. Caputo, *Chem. Commun.*, 1463 (1968).
(3) Two other syntheses of 3-phospholanone oxides, and observations of high enolic content, have since been reported: (a) R. Bodalski and K. Pietrusiewicz, *Tetrahedron Lett.*, 4209 (1972); (b) D. G. Smith and D. J. H. Smith, *ibid.*, 1249 (1973).
(4) J. J. Breen, S. I. Featherman, L. D. Quin, and R. C. Stocks, *Chem. Commun.*, 657 (1972).
(5) G. A. Gray and S. E. Cremer, *J. Org. Chem.*, **37**, 3458 (1972).
(6) G. C. Levy and G. L. Nelson, "Carbon-13 Nuclear Magnetic Resonance for Organic Chemists," Wiley-Interscience, New York, N. Y., 1972: (a) p 110; (b) p 63.
(7) J. H. Billman, S. A. Sojka, and P. R. Taylor, *J. Chem. Soc., Perkin Trans. 2*, 2034 (1972).
(8) The oxidation state of phosphorus has but little influence on the ^{13}C shifts of attached carbons,[4,9] although the coupling constants are strongly affected.
(9) G. A. Gray and S. E. Cremer, *J. Org. Chem.*, **37**, 3470 (1972).
(10) J. B. Stothers, C. T. Tan, A. Nickon, F. Huang, R. Sridhar, and R. Weglein, *J. Amer. Chem. Soc.*, **94**, 8582 (1972).
(11) H. Stetter, "Newer Methods of Preparative Organic Chemistry," W. Foenst, Ed., Academic Press, New York, N. Y., 1963, p 51.
(12) M. Vandewalle, N. Schamp, and H. DeWilde, *Bull. Soc. Chim. Belg.*, **75**, 648 (1966).
(13) L. D. Quin, J. P. Gratz, and T. P. Barket, *J. Org. Chem.*, **33**, 1034 (1968).
(14) G. H. Alt in "Enamines: Synthesis, Structure, and Reactions," A. G. Cook, Ed., Marcel Dekker, New York, N. Y., 1969, p 124.
(15) M. Chattha and A. Aguiar, *J. Org. Chem.*, **38**, 820 (1973).
(16) A. Cook and C. Schutz, *J. Org. Chem.*, **32**, 473 (1967).
(17) H. Fritzsche, U. Hasserodt, and F. Korte, *Chem. Ber.*, **98**, 171 (1965).
(18) L. D. Quin, J. J. Breen, and D. K. Myers, *J. Org. Chem.*, **36**, 1297 (1971).
(19) R. Benkeser and W. Smith, *J. Amer. Chem. Soc.*, **91**, 1556 (1969).
(20) L. D. Quin, J. W. Russell, R. D. Prince and H. E. Shook, Jr., *J. Org. Chem.*, **36**, 1495 (1971).
(21) L. D. Quin and D. A. Mathewes, *J. Org. Chem.*, **29**, 836 (1964).
(22) Nmr spectroscopic analysis of the reaction product of 1-methyl-3-phospholanone (**15**) with morpholine reveals that **13** is formed directly from these reactants.

Photochemical α Cleavage and Free-Radical Reactions of Some Deoxybenzoins[1a,b]

H.-G. Heine,*[1c] W. Hartmann,[1c] D. R. Kory,[1d,e] J. G. Magyar,[1d,e] C. E. Hoyle,[1d] J. K. McVey,[1d] and F. D. Lewis*[1d]

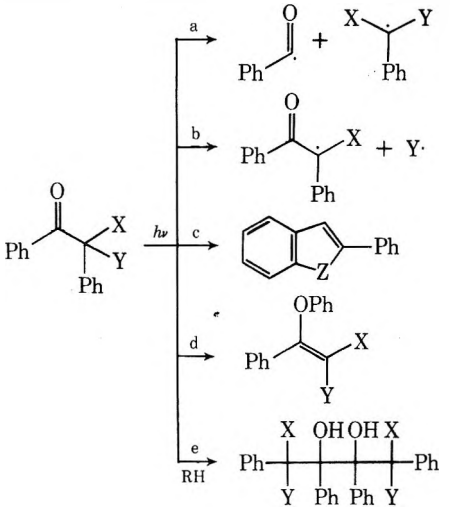
Zentralbereich Forschung, Wissenschaftliches Hauptlaboratorium der Bayer AG, 415 Krefeld-Uerdingen, Germany, and the Department of Chemistry, Northwestern University, Evanston, Illinois 60201

Received September 13, 1973

The effect of α-methyl and α-phenyl substituents on the photochemical α-cleavage reactions of alkyl phenyl ketones has been investigated. α cleavage is the only primary process observed upon irradiation of the deoxybenzoins **1**–**4** in degassed benzene solution. Photoreduction competes with α cleavage of deoxybenzoin in 2-propanol–benzene solution. The reactions of the benzoyl and benzyl free radicals formed upon α cleavage have been studied in some detail. Spectroscopic and energy transfer data indicate that α cleavage occurs exclusively from the lowest $^3n,\pi^*$ excited state. Triplet lifetimes were measured by Stern–Volmer analysis of product quenching by naphthalene and, for deoxybenzoin, by quenching of room temperature phosphorescence. The effects of substituents upon triplet lifetimes indicate that the rate constants do not depend on the stability of the resulting radicals. From a comparison of the rate constants for photochemical α cleavage of the deoxybenzoins studied and the rate constants for thermolysis of corresponding peresters it is concluded that the transition state for α cleavage resembles the excited ketone rather than the radical pair.

The photochemical reactions of benzoin, deoxybenzoin, and their derivatives have received sporadic attention since the early days of organic photochemistry.[2-17] Particularly intriguing are the reports that these compounds undergo a wide variety of reactions (Scheme I), the nature of which depends on both substituents and solvent. For example, benzoin,[3,4] benzoin ethers,[5,6] deoxybenzoin,[7-9] α-alkyl- and α-phenyldeoxybenzoin,[9-11] and 2-phenyl-1-indanone[12] undergo photochemical α cleavage (path a) whereas desyl chloride[13] and sulfides[10,14] undergo β cleavage (path b). Some benzoin esters and desyl amine salts yield 2-phenylbenzofuran,[13,15] and desyl sulfides yield 2-phenylbenzo[*b*]thiophene when irradiated in hydrogen-donor solvents (path c).[14] α,α-Diphenyldeoxybenzoin undergoes a unique 1,3-phenyl shift to give a vinyl ether (path d) along with lesser amounts of α cleavage products (path a).[16] Deoxybenzoin forms a mixture of diastereomeric pinacols when irradiated in hydrogen-donor solvents (path e).[17-20]

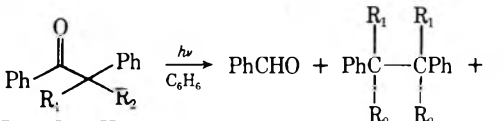
Scheme I
Photochemical Reactions of Deoxybenzoins



In spite of the widespread interest in the preparative photochemistry of these compounds, there are few quantitative data available concerning the effect of structure on photochemical reactivity. Thus the ability to predict which of the primary photochemical processes shown in Scheme I will be the most efficient for a given compound is rather limited. In view of our interest in the photochemical α cleavage reactions of aryl alkyl ketones,[5,9,16,21-24] we have undertaken a detailed investigation of the photochemical behavior of deoxybenzoins. In the present paper the effect of α-methyl and α-phenyl substituents on the reactivity of deoxybenzoin is described. Subsequent papers in this series will deal with the effects of aromatic substituents on the reactivity of deoxybenzoin and the photochemistry of benzoin ethers.

Results

Product Studies and Quantum Yields. Irradiation of deoxybenzoin (**1**) in degassed benzene solution results in the formation of benzaldehyde, benzil, bibenzyl, and toluene (eq 1). Ketones **2**–**4** give analogous products along with styrene and α-methylstyrene in the case of **2** and **3**, respectively. The products were identified by comparison of spectral properties and vpc retention times with those of authentic samples. No attempt was made to identify the higher molecular weight products which result from prolonged irradiation or irradiation in the presence of oxygen.[7]



1, $R_1 = R_2 = H$
2, $R_1 = H$; $R_2 = CH_3$
3, $R_1 = R_2 = CH_3$
4, $R_1 = H$; $R_2 = Ph$

(1)

Bibenzyl is the major product formed upon irradiation of a 0.03 *M* benzene solution of ketone **1** at low conversions. Quantum yields for bibenzyl formation are dependent on light intensity, per cent conversion, and the presence or absence of oxygen. The variation in quantum yield (313-nm irradiation) with conversion at two different light intensities is shown in Figure 1.[25] The quantum yields decrease to half their extrapolated initial values at <5% conversion. The extrapolated quantum yields are 0.18 for $I = 1.7 \times 10^{-6}$ einstein $l.^{-1}$ sec^{-1} and 0.13 for $I = 1.0 \times 10^{-6}$ einstein $l.^{-1}$ sec^{-1}. At the former light intensity and 1% conversion the benzaldehyde quantum yield is 0.050.

In view of the low quantum yields for bibenzyl and benzaldehyde formation from ketone **1**, it appeared likely that cage[24] and/or noncage recombination of benzyl and

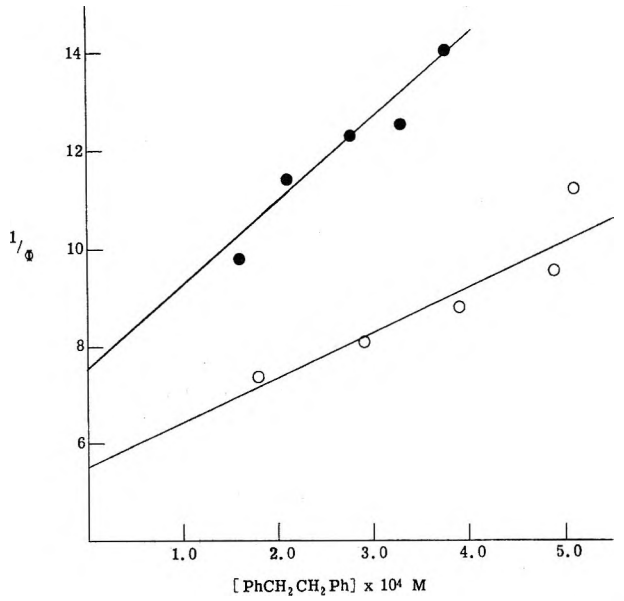
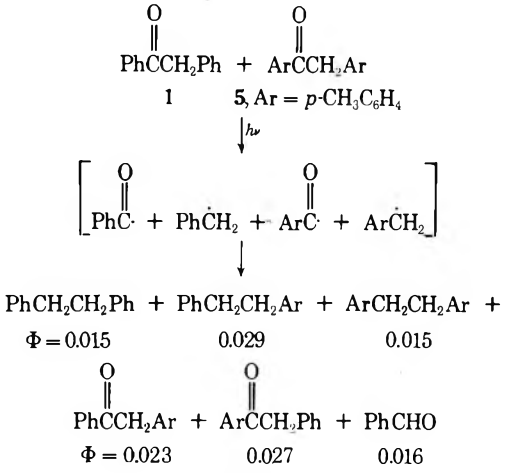


Figure 1. Variation in quantum yield for bibenzyl formation from deoxybenzoin with conversion: ●, $I = 1.7 \times 10^{-6}$ einstein $l.^{-1}$ sec^{-1}; ○, $I = 1.0 \times 10^{-6}$ einstein $l.^{-1}$ sec^{-1}.

benzoyl radicals occurs. In order to assess the extent of noncage recombination, an equiabsorbing mixture of ketone **1** and 4,4′-dimethyldeoxybenzoin (**5**) was irradiated to ~5% conversion (313 nm, 3.8×10^{-6} einstein $l.^{-1}$ sec^{-1}). Fortuitously, **1** and **5** have similar quantum yields for bibenzyl formation under these conditions (0.058 and 0.048, respectively). The results shown in Scheme II indicate that the efficiency of crossover ketone formation ($\Phi = 0.050$) is comparable to that for bibenzyl formation ($\Phi = 0.059$) and greater than that for benzaldehyde formation.

Scheme II



In order to simplify the product mixtures resulting from irradiation of ketones **1**–**4**, low concentrations of 1-dodecanethiol (RSH) were added to the solutions. Figures 2 and 3 show the dependence of product quantum yields on thiol concentration for ketones **1** and **3** (~2% conversion). The benzaldehyde quantum yields increase to a maximum value at 2×10^{-3} *M* RSH. The quantum yield for benzaldehyde formation from ketone **1** appears to decrease at higher thiol concentration; however, no decrease is observed for ketone **2** up to 0.05 *M* thiol[24] and for ketone **3** up to 0.10 *M* thiol. The decrease in bibenzyl quantum yield[25] from ketone **1** with added thiol (Figure 2) is accompanied by increased toluene formation. The quantum yields for cumene formation from ketone **3** increases with

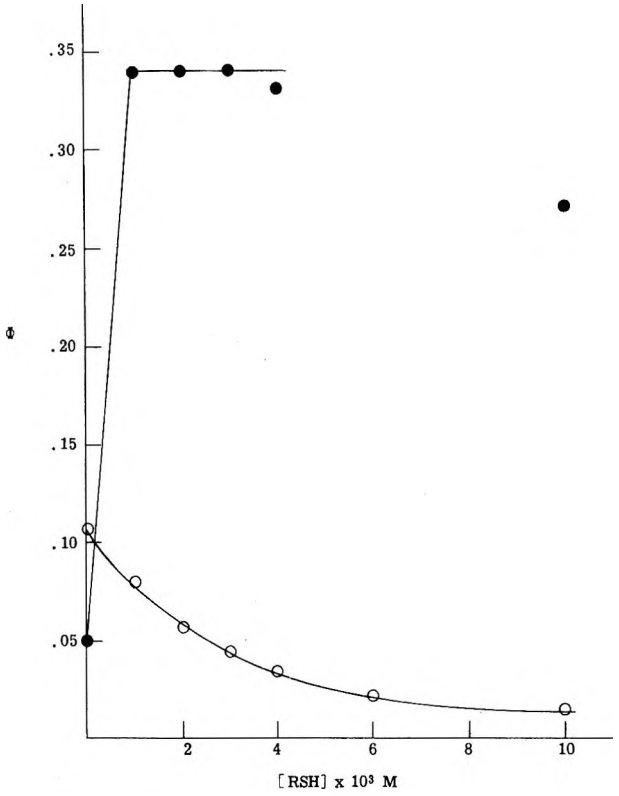


Figure 2. Effect of added dodecanethiol on quantum yields for benzaldehyde (●) and bibenzyl (○) formation from deoxybenzoin.

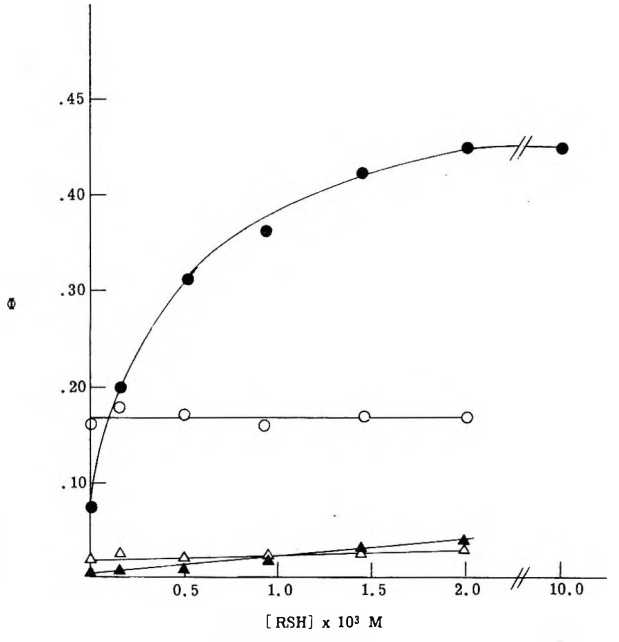


Figure 3. Effect of added dodecanethiol on quantum yields for benzaldehyde (●), bicumyl (○), cumene (▲), and α-methylstyrene (△) formation from α,α-dimethyldeoxybenzoin.

added thiol whereas the values for bicumyl- and α-methylstyrene remain constant (Figure 3). Addition of 0.03 *M* thiol to a mixture of ketones **1** and **5** completely suppresses the formation of crossover ketones.

Maximum quantum yields for benzaldehyde formation from ketones **1**–**3** were determined by irradiating 3×10^{-2} *M* benzene solutions containing 3×10^{-3} *M* thiol to varying conversions. The dependence of $1/\Phi$ with conversion (expressed in terms of benzaldehyde concentration) for ketones **1** and **2** is shown in Figure 4. The decrease in quantum yield for ketone **2** is more gradual than for ke-

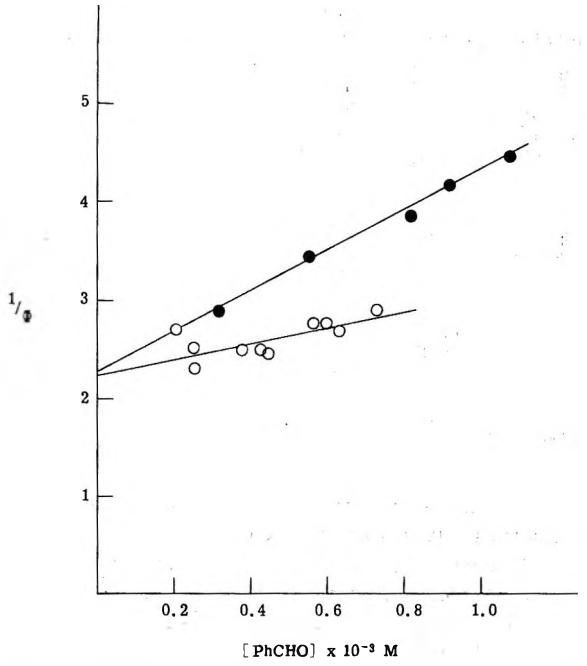


Figure 4. Variation in quantum yield for benzaldehyde formation from deoxybenzoin (●), and α-methyldeoxybenzoin (○) with conversion.

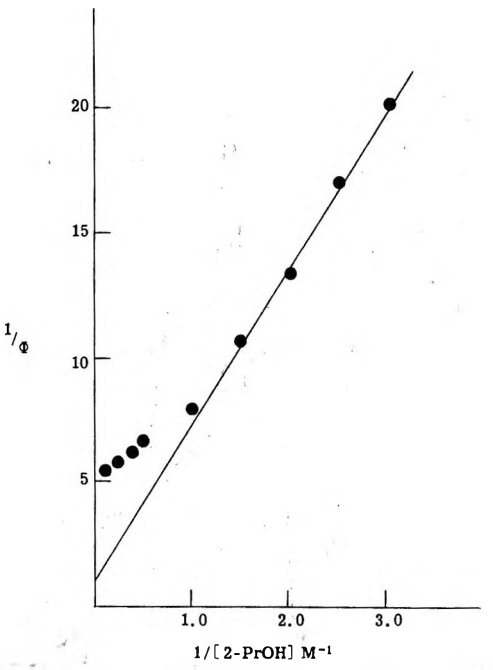


Figure 5. Dependence of quantum yield for deoxybenzoin photoreduction with 2-propanol concentration.

tone **1**, and the value for ketone **3** is invariant up to several per cent conversion. Quantum yields extrapolated to zero conversion are given in Table I.

Table I
Quantum Yields and Kinetic Data

Ketone	Solvent	Φ^a	$k_q\tau$, M^{-1} [b]	$1/\tau \times 10^{-7}$, sec^{-1}
$PhCOCH_2Ph$ (**1**)	C_6H_6		2100	0.24
	C_6H_6–RSH	0.44	3100	0.16
$PhCOCH(CH_3)Ph$ (**2**)	C_6H_6		170	2.9
	C_6H_6–RSH	0.44	240	2.1
$PhCOC(CH_3)_2Ph$ (**3**)	C_6H_6		33	15
	C_6H_6–RSH	0.45	42	12
$PhCOCHPh_2$ (**4**)	C_6H_6		50	10

[a] Quantum yield for benzaldehyde formation in 3×10^{-3} M dodecanethiol–benzene extrapolated to zero conversion, ±5%. [b] Slopes of linear Stern–Volmer plots for naphthalene quenching, ±35% for ketone **1**, ±15% for ketones **2–4**.

Kinetics. Irradiation of ketones **1–4** in the presence of conjugated dienes, biphenyl, or naphthalene diminishes the quantum yields for product formation. Curved Stern–Volmer quenching plots were obtained for diene quenchers, presumably due to reaction of the free radical products with the diene. Biphenyl (313-nm irradiation) and naphthalene (365-nm irradiation) both gave linear Stern–Volmer plots; however, the slope ($k_q\tau$) for the biphenyl quenching plot is two to three times less than that for naphthalene quenching. This is indicative of quenching at less than the diffusion-controlled rate by biphenyl.[26a] Thus naphthalene proved to be the most satisfactory quencher in spite of the necessity of irradiating at wavelengths >330 nm to avoid competitive absorption by quencher. Sufficient naphthalene was used to quench between 30 and 60% of product formation. This required naphthalene concentrations of $\sim 10^{-4}$ M for ketone **1** and $\sim 10^{-2}$ M for ketones **3** and **4**. The slopes of individual Stern–Volmer plots were determined by the method of least squares and had correlation coefficients of 0.98 or better. The slopes of linear Stern–Volmer plots for naphthalene quenching of benzaldehyde formation decrease with increasing conversions. As is the case for the benzaldehyde quantum yields (Figure 4), the effect is greatest for ketone **1**. This results in a larger error in the value of $k_q\tau$ for ketone **1** than for ketones **2–4**.

Table II
Absorption Spectral Data for Phenyl Ketones PhCO–R

Compd	R	Cyclohexane λ_{max}, nm	Cyclohexane (ε)	Ethanol λ_{max}, nm	Ethanol (ε)
6	CH_3	323	(40)	316	(63)
7	$C(CH_3)_3$	321	(89)	317	(130)
1	CH_2Ph	323	(126)	321	(160)
2	$CH(CH_3)Ph$	323	(168)	321	(210)
3	$C(CH_3)_2Ph$	325	(140)	320	(170)
4	$CHPh_2$	327	(200)	324	(196)

The $k_q\tau$ values given in Table I are the slopes of Stern–Volmer quenching plots obtained at <1% conversion both with and without added thiol. The data obtained without added thiol are the average of four or more Stern–Volmer plots. The data for ketone **1** with added thiol are the average of six Stern–Volmer plots with a standard deviation of 35%. The error limits for ketones **2–4** are considerably smaller (±15%). The $1/\tau$ values in Table I are calculated assuming $k_q = 5 \times 10^9$ M^{-1} sec^{-1} for naphthalene quenching. By analogy to the results of Wagner[26b] for quenching of valerophenone and α,α-dimethylvalerophenone, we assume that there is no steric effect on the rate constant for energy transfer.

Irradiation of ketone **1** in 2-propanol–benzene solution results in the formation of acetone and a mixture of stereoisomeric pinacols[17-20] in addition to the products of α cleavage. The variation in the quantum yield for acetone formation with 2-propanol concentration is shown in Figure 5. The linear portion of the line obtained for 2-propanol concentrations <1 M has a slope of 6.4 ± 0.1 M and an intercept of 1.0 ± 0.2. The deviation from linearity at higher 2-propanol concentrations is similar to that observed for acetophenone photoreduction.[27,28]

Spectroscopic Data. The ultraviolet absorption data for ketones **1–4** in cyclohexane and ethanol solvent are given in Table II along with values for acetophenone (**6**) and pivalophenone (**7**). Emission spectra were recorded at 77°K in both polar and nonpolar glasses. Structured emis-

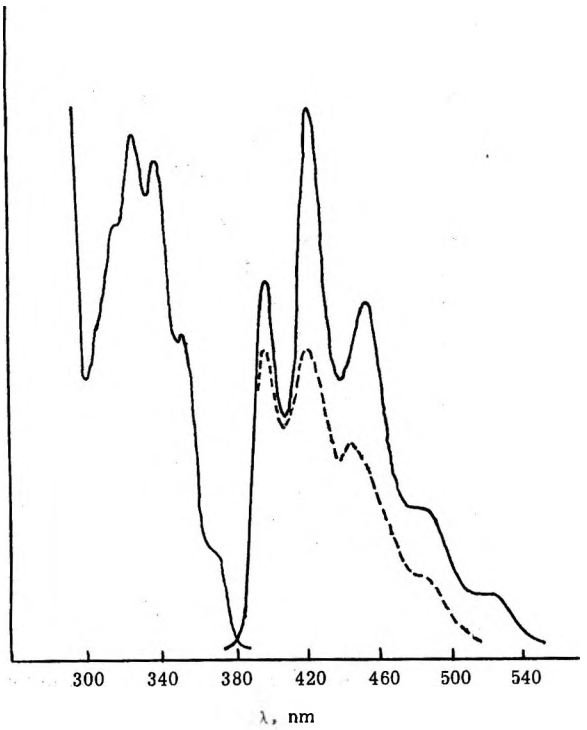


Figure 6. Room temperature absorption (——), emission (- - -), and 77°K emission (——) spectra of deoxybenzoin (arbitrary intensities).

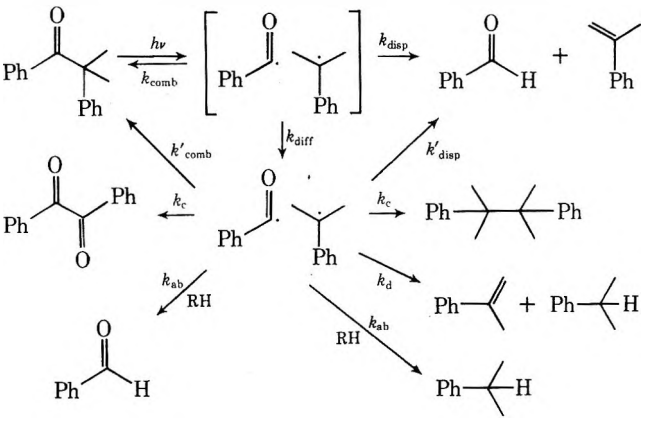
sion similar to that for acetophenone or pivalophenone was observed for ketones **2–4**. The positions of the emission maxima for ketone **1** in EPA agree with a previous report.[29] Triplet energies are estimated from the position of the highest energy emission maxima and are the same in MC and MP glasses. Triplet lifetimes were determined by flash-emission studies at 77°K. Emission from ketones **2–4** and **7** occurs predominantly from a single short-lived excited state (τ < 10 msec) in both polar and nonpolar solvents. Intersystem crossing quantum yields for ketones **2–4** and **7** were determined by the method of Lamola and Hammond.[30] Comparison of the extent of trans → cis piperylene isomerization to that for benzophenone (Φ = 1.0) gave values of 1.0 ± 0.05 for all of the ketones studied.

Room temperature emission was observed from highly degassed carbon tetrachloride or benzene solutions of ketones **1** and **6**. Room temperature emission of ketone **6** has previously been observed[31] and is considerably more intense than that for ketone **1**. The room temperature and 77°K emission spectra and absorption spectrum of ketone **1** are shown in Figure 6. The position of the emission maxima at 77°K and at room temperature are quite similar. Quenching of the room temperature emission in benzene by 2,5-dimethyl-2,4-hexadiene yields a value of $1/\tau$ = 1.2 ± 0.2 × 10^6 sec^{-1}, in excellent agreement with the values obtained by product quenching (Table I). The room temperature emission of ketone **1** was also quenched by 1-dodecanethiol. From the slope of the phosphorescence quenching plot ($k_q\tau$ = 37 M^{-1}) and the triplet lifetime, a value of k_q = 4.4 ± 1.5 × 10^7 M^{-1} sec^{-1} for thiol quenching is obtained.

Discussion

Free Radical Reactions. The products observed upon irradiation of ketones **1–4** in benzene solution (eq 1) can be accounted for in terms of a general mechanism shown in Scheme III for ketone **3**. There is no evidence for products arising from any photochemical process other than α cleavage and the subsequent free radical reactions. We will concern ourselves first with the cage and noncage

Scheme III
Reactions of the Photochemically Generated Radical Pair



reactions of the benzoyl radical and subsequently with the nature of the excited state and α cleavage process.

Possible cage reactions of the initially formed radical pair include recombination to give ground state ketone (k_{comb}), diffusion to give separated free radicals (k_{diff}), and, in the case of ketones **2** and **3**, disproportionation to benzaldehyde and styrene or α-methylstyrene (k_{disp}). Since α cleavage occurs from a triplet state (*vide infra*) cage recombination and disproportionation require spin inversion prior to bond formation. Salem[32] has recently shown that a triplet diradical state is nearly degenerate with the singlet diradical. Thus there should be no spin-correlation effect[33] on the radical pair cage reactions. In accord with Salem's theory we have found cage recombination of optically active ketone **2** to account for at least one-third of the initially excited molecules.[24] Cage disproportionation may be responsible for some of the benzaldehyde from **2** and **3** and the excess of α-methylstyrene over cumene from **3** in the absence of thiol scavenger (Figure 3, $\Phi_{disp} \leq 0.02$).

Noncage radical reactions include recombination of benzoyl and benzyl radicals to give ground state ketone (k'_{comb}). The formation of crossover ketones upon irradiation of a mixture of ketones **1** and **5** (Scheme II) indicates the importance of this reaction in the absence of added thiol. Since the quantum yields for crossover ketone and bibenzyl formation are comparable, the rate constant for benzoyl–benzyl combination must be comparable to the known rate constant for benzyl–benzyl combination (4.1 × 10^9 M^{-1} sec^{-1}).[34] Noncage disproportionation (k'_{disp}) of benzoyl–cumyl radical pairs from ketone **3** cannot be very important in view of the low α-methylstyrene quantum yield and its insensitivity to added thiol (Figure 3).

In addition to reactions with benzyl radicals, benzoyl radicals can combine to form trace amounts of benzil (k_c) or abstract hydrogen to form benzaldehyde (k_{ab}). Similarly, benzyl radicals can combine or abstract hydrogen, and the 1-phenylethyl and cumyl radicals can disproportionate. The quantum yields for cumene and bicumyl formation from ketone **3** provide a value of 0.059 for the disproportion/combination ratio of the cumyl radical. This result is in excellent agreement with the value 0.054 reported by Nelsen and Bartlett.[35]

Addition of low concentrations of dodecanethiol (RSH) to the benzene solvent greatly increases the quantum yields for benzaldehyde formation (Figures 2 and 3) and thereby simplifies quantitative study of the α cleavage reaction.[22-24,36] The ability of thiol to scavenge all of the noncage benzoyl radicals (eq 2) is indicated by the total supression of crossover ketone formation from ketones **1**

$$PhCO + RSH \longrightarrow PhCHO + RS\cdot \quad (2)$$

Table III
Phosphorescence Data for Phenyl Ketones

Compd	R	Solvent	E_T, kcal/mol	τ, msec
6	CH_3[a]	MC[b]	73.5	4
		EtOH	74.0	8.0
		CCl_4[c]	72.0	
7	$C(CH_3)_3$	MC	71.5	3.7
		EPA[d]	72.2	4.9
1	CH_2Ph	MC	72.0	1.9
		EPA	73.3	2.8
		C_6H_6[c]	72.0	
2	$CH(CH_3)Ph$	MC	73.0	2.9
		EPA	73.3	4.6
3	$C(CH_3)_2Ph$	MC	73.0	4.1
		EPA	73.0	6.1
4	$CHPh_2$	MP[e]	72.4	

[a] Data from ref 44. [b] Methylcyclohexane. [c] Room temperature emission. [d] Ether–isopentane–ethanol. [e] Methylcyclohexane–isopentane.

and 5 (Scheme II) by 3×10^{-2} *M* RSH and by the maximization of benzaldehyde quantum yields with $\sim 10^{-3}$ *M* RSH (Figures 2 and 3). Possible complications arising from the use of thiols include reactions of the thiyl radical and quenching of the excited state by thiol. The abstraction reaction (eq 2) is known to be approximately thermoneutral.[37] The thiyl radicals formed do not initiate the decarbonylation of benzaldehyde as they do for aliphatic aldehydes.[38] Zepp and Wagner[39] have reported that thiols quench the $^3n,\pi^*$ state of acetophenone with a rate constant of 1.4×10^7 M^{-1} sec^{-1}. The rate constant for dodecanethiol quenching of ketone 1 obtained by quenching of room temperature phosphorescence is 4.4×10^7 M^{-1} sec^{-1}. Since we typically used thiol concentrations of 10^{-3} *M*, quenching of ketones with lifetimes shorter than 10^{-6} sec should be insignificant.

The thiol scavenging results shown in Figures 2 and 3 can also be used in conjunction with the known rate constants for benzyl[34] and cumyl[40] radical combination (eq 3 and 4) to provide rate constants for the reaction of benzyl and cumyl radicals with dodecanethiol. A steady-state assumption for benzyl radical gives eq 5, where Φ is the quantum yield for noncage radical formation, *I* is the light intensity, and k_c and k_{SH} are the rate constants for reactions 3 and 4. From the light intensity and a value of $\Phi \approx 0.5$ (Table I), the steady-state concentration of benzyl

$$2PhCH_2\cdot \xrightarrow{k_c} PhCH_2CH_2Ph \quad (3)$$

$$PhCH_2\cdot + RSH \xrightarrow{k_{SH}} PhCH_3 + RS\cdot \quad (4)$$

$$\Phi I = \frac{-d[PhCH_2\cdot]}{dt} = 2k_c[PhCH_2\cdot]^2 + k_{SH}[PhCH_2\cdot][RSH] \quad (5)$$

radicals in the absence of thiol is 1.1×10^{-8} *M*. Estimation of k_{SH} by successive approximation gives a best fit to the experimental data for bibenzyl formation (Figure 2) for a value of $k_{SH} = 3.5 \times 10^4$ M^{-1} sec^{-1}. This value is in good agreement with the rate constant for benzyl radical hydrogen abstraction from α-toluenethiol ($k_{SH} = 5.1 \times 10^4$ M^{-1} sec^{-1}) reported by Burkhart.[34] Similar analysis of the data for cumene formation from ketone 3 gives a value of $k_{SH} = 8.3 \times 10^3$ M^{-1} sec^{-1} for the abstraction reaction of cumyl radical. The smaller rate constant for cumyl *vs.* benzyl radical is expected on the basis of radical stability.

Identity of the Reactive Excited State. The nature of the reactive excited state is of considerable importance in photochemical α cleavage reactions. For example, the lowest triplet state of dialkyl ketones is much more reactive toward α cleavage than the singlet state.[41] The configuration of the lowest triplet state is also important, since it is known that a lowest $^3n,\pi^*$ state is more reactive than a $^3\pi,\pi^*$ state in the case of substituted pivalophenones[23] and 2-phenyl-1-indanones.[12] The ability of naphthalene, biphenyl, and dienes to quench the formation of products from ketones 1–4 indicates that α cleavage occurs from a triplet state. High intersystem crossing quantum yields establish that triplet formation occurs with unit efficiency. The n,π^* absorption spectra of ketones 2–4 and pivalophenone (7) are much more intense than that of acetophenone (6) (Table II). The exhalted n,π^* absorption of α-phenyl ketones has been attributed to interaction of the n,π^* state with the adjacent π electrons.[42,43] This interaction could lead to a lowest n,π^* triplet with substantial π,π^* character or a lowest π,π^* triplet. In either case a decrease in reactivity compared to pivalophenone would be expected.

The low temperature emission spectra of ketones 1–4 are highly structured (Figure 6) and similar in appearance to those of ketones 6 and 7. Ketones 1–4 and 7 display predominantly short-lived emission in both polar and nonpolar glasses (Table III). Such emission is characteristic of phenyl ketone $^3n,\pi^*$ states.[44] The weak room temperature emission of ketone 1 in benzene is less well resolved than the low temperature emission (Figure 6); however, the emission maxima occur at similar wavelengths. Thus the lowest energy triplet state both at room temperature and at 77°K is the $^3n,\pi^*$ state.

Transition State for α Cleavage. The formation of benzaldehyde from ketones 1–4 can be described by the abbreviated mechanism given in eq 6-9

$$D \xrightarrow{h\nu} {}^1D \xrightarrow{k_{ST}} {}^3D \quad (6)$$

$${}^3D \xrightarrow{k_d} D \quad (7)$$

$${}^3D + Q \xrightarrow{k_q} D + {}^3Q \quad (8)$$

$${}^3D \xrightarrow{k_\alpha} PhC\dot{O} + PhC\dot{R}_1R_2 \xrightarrow{RSH} PhCHO \quad (9)$$

where D is the deoxybenzoin and Q is the quencher naphthalene. Since the $^3n,\pi^*$ state is formed with unit efficiency, the quantum yield for benzaldehyde formation is determined by the efficiency of α cleavage and the probability (β) that the benzoyl radical will form benzaldehyde. The ratio of the quantum yield expressions with and without added quencher (eq 10 and 11) gives the Stern-Volmer equation (eq 12). The probability factor β should not change upon addition of quencher and thus will not affect lifetimes determined by Stern-Volmer kinetics. Evidence has recently been presented that cage recombination of benzoyl and benzyl radicals rather than nonradiative decay of the $^3n,\pi^*$ state is responsible for the inefficiency in product formation from ketone 2.[24] Thus the triplet lifetimes obtained from Stern-Volmer quenching experiments (Table I) are determined by the rate constant for α cleavage ($k_\alpha = 1/\tau$).

$$\Phi^0 = \left(\frac{k_\alpha}{k_\alpha + k_d}\right)\beta \quad (10)$$

$$\Phi = \left(\frac{k_\alpha}{k_\alpha + k_d + k_q[Q]}\right)\beta \quad (11)$$

$$\frac{\Phi^0}{\Phi} = 1 + \frac{k_q[Q]}{k_\alpha + k_d} = 1 + k_q\tau[Q] \quad (12)$$

The kinetic data in Table I show that the triplet lifetimes decrease with substitution of either methyl or phenyl groups at the α carbon. Such a trend would be expected if the rate constant for α cleavage is determined by the stability of the radical pair. It has been commonly assumed that reactivity toward α cleavage is determined by the stability of the radicals produced;[45] however, evidence concerning the free radical character of the transition

Table IV
Rate Constants for Photochemical α Cleavage and Perester Thermolysis[a]

R	PhC(=O)R, $k_\alpha^{22°} \times 10^{-7}$ sec^{-1}	Registry no.	RC(=O)OO-*t*-Bu, $k_{therm}^{60°} \times 10^{4}$, sec^{-1}	Registry no.
$-CH(CH_3)_2$	0.034[b,c]	611-70-1	0.069	109-13-7
$-C(CH_3)_3$	1.1[b]		2.3	927-07-1
$-CH_2Ph$	0.16		0.41	3377-89-7
$-CH(CH_3)Ph$	2.1		5.8	3377-90-0
$-C(CH_3)_2Ph$	12		58	24161-29-3
$-CHPh_2$	10		27	13144-32-6

[a] Values from ref 48. [b] Values from ref 23. [c] See ref 49.

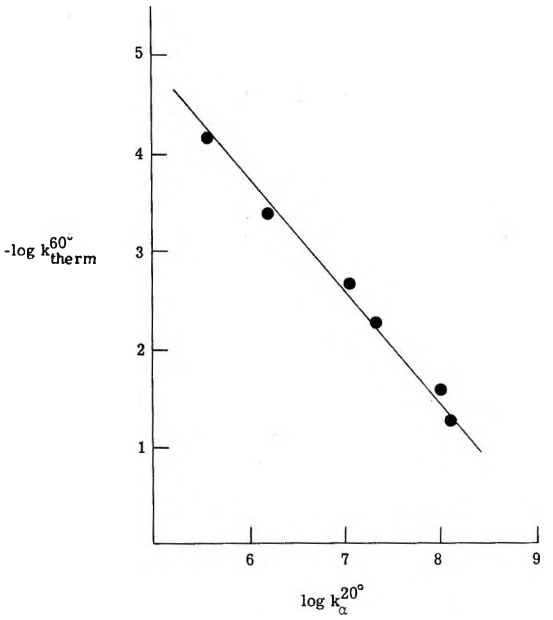
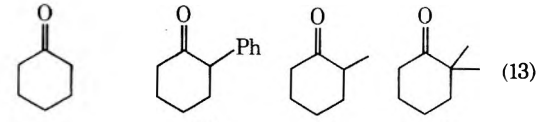
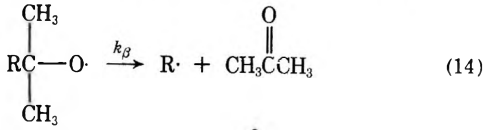


Figure 7. Linear free-energy relationship of photochemical α cleavage [PhC(=O)R] and perester thermolysis [RC(=O)OO-*t*-Bu].

state is lacking. Consideration of bond dissociation energies[22] indicates that α cleavage of ketones **1**–**4** is exothermic. Thus, according to the Hammond principle,[46] the transition state should more nearly resemble the ketone excited state than the radical pair. The faster α cleavage rate constant for pivalophenone (**7**) *vs.* deoxybenzoin is clearly contrary to predictions based on radical stability. There are several previous reports of homolytic cleavage reactions in which *tert*-alkyl compounds are more reactive than benzyl compounds. Among these are the photochemical α cleavage reactions of cyclohexanones (eq 13),[45b] the β-scission reaction of alkoxy radicals (eq 14),[47] and perester thermolysis (eq 15 and Table IV).[48]

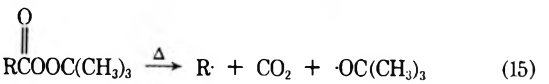


(13)



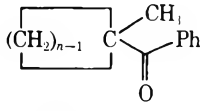
(14)

k_β: *t*-Bu > *i*-Pr > $PhCH_2$ > Et > Me

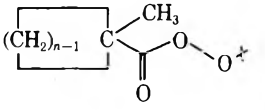


(15)

Rüchardt's[48] extensive studies of homolytic cleavage reactions have resulted in several criteria for determining the position of the transition state along the reaction coordinate. One criterion involves the relative effects of α-methyl and α-phenyl substituents upon reaction rate. Tertiary alkyl radicals are always formed more rapidly than secondary or primary, even when bond breaking is not far advanced in the transition state. However, substantial rate acceleration upon α-phenyl substitution requires a radical-like transition state. Rüchardt has presented convincing evidence that the perester C_α–CO bond is only insignificantly lengthened in the transition state (eq 15). Since radical character is not highly developed, the stability of the benzyl radical is not reflected in the rate of thermolysis. Thus comparison of our results for α cleavage of phenyl ketones with Rüchardt's studies of perester decomposition should be particularly informative. The free energy relationship for the data given in Table IV is shown in Figure 7. The linearity of this relationship (correlation coefficient = 0.996) indicates that substituents have similar effects on the transition states for both reactions. A second criterion for the position of the transition state along the reaction coordinate is the effect of ring size on reaction rate. Both photochemical α cleavage of α-methyl cycloalkyl ketones[50] and the corresponding peresters[48c] have larger rate constants for six-membered than for five-membered rings. Since the introduction of an sp^2



$k_5/k_6 \approx 0.1$



$k_5/k_6 = 0.33$

center in a cycloalkane ring produces a larger decrease in conformational strain for five-membered than for six-membered rings, a value of $k_5/k_6 > 1$ would be expected if the transition states had substantial free radical character.

From the preceding analogies with perester thermolysis, we conclude that *the transition states for α cleavage of phenyl ketones* **1**–**4** *and* **7** *lie early on the reaction coordinate.* It should be emphasized that increased reactivity toward α cleavage with increasing substitution at the α carbon is due mainly to ground state steric effects[48] rather than increased stability of the product radical pair.[45] The results of Wagner[45b] for α cleavage of cyclohexanones indicate that this conclusion may apply to photochemical α cleavage reactions in general.

As previously mentioned, an alternative explanation of the decreased reactivity of ketone **1** *vs.* **7** is that the α-phenyl group alters the triplet energy or the configuration of the lowest triplet state. Although the spectroscopic data do not support such an explanation, it was further explored by studying the photoreduction of ketone **1**. Photoreduction rate constants for aryl ketones are known to be sensitive to the configuration of the lowest triplet state.[23,51] Incorporation of photoreduction (eq 16) into the previous kinetic scheme (eq 6–9) gives the relationship between the quantum yield for acetone formation and 2-propanol (RH) concentration in eq 17. A plot Φ^{-1} *vs.*

$[RH]^{-1}$ is linear for 2-propanol concentrations less than 1.0 M and has an intercept of 1.0 (Figure 5). The nonlinearity at higher 2-propanol concentrations is similar to that observed for photoreduction of acetophenone.[52] From the slope of the linear portion of Figure 5 and the triplet lifetime from Table I, a value of $k_r = 2.5 \times 10^5\ M^{-1}\ sec^{-1}$ is obtained. This value is similar to that for propiophenone ($4.4 \times 10^5\ M^{-1}\ sec^{-1}$) and distinctly faster than those for isobutyrophenone ($0.9 \times 10^5\ M^{-1}\ sec^{-1}$) and pivalophenone ($0.24 \times 10^5\ M^{-1}\ sec^{-1}$).[23] Thus it seems highly unlikely that the lowest triplet of deoxybenzoin has more $^3\pi,\pi^*$ character than the lowest triplet of pivalophenone.

$$^3D + (CH_3)_2CHOH \xrightarrow{k_r} PhC(OH)CH_2Ph + (CH_3)_2\dot{C}OH \longrightarrow PhCH_2C(OH)(Ph)-C(OH)(Ph)CH_2Ph + (CH_3)_2C{=}O \quad (16)$$

$$\frac{1}{\Phi} = 1 + \frac{k_\alpha + k_d}{k_r[RH]} = 1 + \frac{1}{k_r\tau[RH]} \quad (17)$$

One final aspect of our results that warrants discussion is the unusually marked decrease in product quantum yields with increasing conversion (Figures 1 and 4).[53] This behavior provides one of the few examples of efficient quenching by a photoproduct.[54,55] Incorporation of benzaldehyde (B) quenching (eq 18) into the previous kinetic scheme (eq 6–9) gives eq 19.[55b]

$$^3D + B \xrightarrow{k_{qp}} D + {}^3B \quad (18)$$

$$\frac{1}{\Phi_B} = \frac{1}{\Phi_B^0}\left(1 + \frac{k_{qp}\tau[B]}{2}\right) \quad (19)$$

The slope/intercept ratios from Figure 4 give $k_{qp}\tau$ values of 1700 and 72 M^{-1} for ketones **1** and **2**. Using the triplet lifetimes in Table I, the apparent rate constants[55b] for quenching of ketones **1** and **2** by benzaldehyde are both $\sim 2 \times 10^9\ M^{-1}\ sec^{-1}$. Owing to its relatively long triplet lifetime, ketone **1** is more sensitive to product quenching than are ketones **2–4**. Product quenching decreases lifetimes measured by Stern–Volmer quenching as well as quantum yields. This problem was minimized by conducting quenching studies at <1% conversion. The excellent agreement of the lifetimes measured by naphthalene quenching of product formation and 2,5-dimethyl-2,4-hexadiene quenching of room temperature phosphorescence for ketone **1** indicates that the product quenching data in Table I are reliable. However, it should be borne in mind that quantum yield and kinetic data for reactions in which a product quenches the excited state precursor must be extrapolated to zero conversion.

Experimental Section

Ketones and Solvents. Deoxybenzoin (**1**) was either a commercial sample (Aldrich) or prepared *via* Friedel–Crafts acylation of benzene with phenylacetyl chloride, mp 55–56°. α-Methyldeoxybenzoin (**2**) was prepared by the method of Meyer and Oelkers,[56] mp 51° (lit.[56] 53°). α,α-Dimethyldeoxybenzoin (**3**) was prepared by alkylation of deoxybenzoin with sodium hydride and methyl iodide or by the reaction of α,α-dimethylbenzyl cyanide with phenylmagnesium bromide,[57] mp 45–46° (lit.[57] mp 46–47°). α-Phenyldeoxybenzoin (**4**) was prepared by Friedel–Crafts alkylation of benzene with desyl chloride, mp 136–137° (lit.[58] 135–136°). 4,4′-Dimethyldeoxybenzoin (**5**), 4-methyldeoxybenzoin, and 4′-methyldeoxybenzoin were all synthesized by Grignard reactions of benzylmagnesium chloride or 4-methylbenzylmagnesium chloride with benzaldehyde or *p*-tolualdehyde, mp 101° (lit.[59] 102°), mp 96° (lit.[60] 97°), and mp 108° (lit.[60] 110°), respectively. All ketones were extensively purified by recrystallization, chromatography on silica gel, or vacuum sublimation. Purity was >99% by vpc in all cases. Naphthalene was purified by sublimation or zone refining. Benzene (thiophene-free or spectrograde) was distilled from sodium wire or phosphorus pentoxide prior to use. Dodecanethiol (Aldrich) was distilled prior to use.

Quantum Yields and Kinetics. For quantum yield measurements, benzene solutions containing $3 \times 10^{-2}\ M$ ketone and $10^{-3}\ M$ tetradecane internal standard were degassed and sealed under vacuum in 13-mm-o.d. Pyrex tubes. The tubes were irradiated on a merry-go-round apparatus at 23 ± 2° using a Hanovia 450-W lamp and a potassium chromate filter solution to isolate the 313-nm mercury line. Light intensities were measured by simultaneous irradiation of benzophenone–benzhydrol[61] and/or potassium ferroxalate[62] actinometers. Both actinometer systems gave the same measured intensities. Product yields were determined by vpc analysis on either a 7 ft × 0.125 in. column of 10% FFAP on DMSC-treated Chromosorb G or a 6 ft × 0.125 in. column of 4% QF1 and 1% Carbowax 20M on Chromosorb G using a Hewlett-Packard 5750 gas chromatograph. Naphthalene quenching studies were conducted both with and without added dodecanethiol. The studies with added thiol were conducted on 0.1 M ketone solutions containing $3 \times 10^{-3}\ M$ thiol in degassed benzene. Corning filters 7-54 and 0-52 were used to isolate 365-nm irradiation. Quenching studies without added thiol were conducted on $5 \times 10^{-2}\ M$ ketone solutions contained in quartz tubes and bubbled with oxygen-free nitrogen for 5 min. Light from a Philips 125-W high pressure mercury lamp was filtered to prevent irradiation at wavelengths shorter than 330 nm. The tubes were analyzed for benzaldehyde and bibenzyl formation on a 2 m × 0.4 cm column of 5% SE-30 on DMSC treated Chromosorb G using a Perkin-Elmer F 20 gas chromatograph. Quantum yields for acetone formation from irradiation of ketone **1** in degassed 2-propanol–benzene were determined as previously described.[28]

Spectroscopic Data. Absorption spectra were recorded on a Cary 14 spectrophotometer. Emission spectra were recorded at 77°K in a 4:1 methylcyclohexane–isopentane (MP) glass using an Aminco-Bowman spectrophotometer and in methylcyclohexane (MC) and 5:5:2 ether–isopentane–ethanol (EPA) using a Perkin-Elmer MPF-2A spectrophotometer. The results obtained in MP and MC with the two different spectrophotometers were identical. Room temperature emission spectra of acetophenone and deoxybenzoin ($10^{-2}\ M$) were recorded on highly degassed samples in sealed Pyrex ampoules at 22° using the Perkin-Elmer spectrophotometer. Quenching of room temperature emission was investigated by adding increasing amounts of 2,5-dimethyl-2,4-hexadiene.

Flash-Emission Kinetics. Phosphorescence lifetimes were measured by a fully computerized, signal averaging approach. The exciting source was a Xenon Corp. micropulse flashtube (pulse width ~5 μsec) with a Model 457 power supply. Light from the flash tubes was filtered by a Corning 7-54 glass filter to reduce scattered light with wavelengths >370 nm. Degassed samples contained in sealed 4-mm-o.d. Pyrex tubes were cooled to 77°K in a quartz dewar. Emitted light was viewed at 90° to the excitation through a 0.25-m Bausch and Lomb grating monochrometer by an EMI Model 6256 photomultiplier. The photomultiplier output was amplified by a series of three Philbrick-Nexus Model 1011 operational amplifiers interfaced to the 40-kHz analog-to-digital converter of a Raytheon 704 on-line digital computer. The computer is programmed to fire the flashtube, acquire the phosphorescence decay data, and compute the lifetime from a least-squares fix of the data. The results in Table III are the average of three or more lifetimes determined at the 0-0 emission band.

Acknowledgment. The authors at Northwestern thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, and PPG Industries for support of this research. We also wish to thank R. P. VanDuyne for his invaluable assistance in obtaining the phosphorescence lifetimes.

Registry No.—**1**, 451-40-1; **2**, 2042-85-5; **3**, 13740-70-0; **4**, 1733-63-7; **6**, 98-86-2; **7**, 938-16-9.

References and Notes

(1) (a) Part V: Photochemical α Cleavage of Ketones in Solution. (b) Part IV: H.-G. Heine, *Tetrahedron Lett.*, 4755 (1972). (c) Bayer AG. (d) Northwestern University. (e) Northwestern University Fellow, 1969–1973.

(2) (a) A. Schönberg, "Preparative Organic Photochemistry," Springer-Verlag New York, New York, N. Y., 1968, Chapters 22 and 23; (b)

H.-G. Heine, H.-J. Rosenkranz, and H. Rudolph, *Angew. Chem., Int. Ed. Engl.*, **11**, 974 (1972).
(3) G. Ciamician and P. Silber, *Ber.*, **34**, 1530 (1901).
(4) G. Kornis and P. de Mayo, *Can. J. Chem.*, **42**, 2822 (1964).
(5) Part IV, ref 1b.
(6) T. Dominh, *Ind. Chim. Belg.*, 36, 1080 (1971).
(7) J. Kenyon, A. R. A. A. Rassoul, and G. Soliman, *J. Chem. Soc.*, 1774 (1956).
(8) G. L. Closs and D. R. Paulson, *J. Amer. Chem. Soc.*, **92**, 7229 (1970).
(9) H.-G. Heine, *Tetrahedron Lett.*, 3411 (1972).
(10) A. Schönberg, A. K. Fateen, and S. M. A. R. Omran, *J. Amer. Chem. Soc.*, **78**, 1224 (1956).
(11) K. Müller and G. L. Closs, *J. Amer. Chem. Soc.*, **94**, 1002 (1972).
(12) A. A. Baum, *J. Amer. Chem. Soc.*, **94**, 6866 (1972).
(13) J. C. Sheehan and R. M. Wilson, *J. Amer. Chem. Soc.*, **86**, 5277 (1964).
(14) J. R. Collier and J. Hill, *Chem. Commun.*, 640 (1969).
(15) J. C. Sheehan, R. M. Wilson, and A. W. Oxford, *J. Amer. Chem. Soc.*, **93**, 7222 (1971).
(16) H.-G. Heine, *Tetrahedron Lett.*, 1473 (1971).
(17) A. Paterno, G. Chieffi, and G. Perret, *Gazz. Chim. Ital.*, **44** I, 151 (1914).
(18) W. D. Cohen, *Chem. Weekbl.*, **13**, 902 (1916).
(19) F. Bergmann and Y. Hirshberg, *J. Amer. Chem. Soc.*, **65**, 1429 (1943).
(20) J. H. Stocker and D. H. Kern, *J. Org. Chem.*, **33**, 1271 (1968).
(21) H.-G. Heine, *Justus Liebigs Ann. Chem.*, **732**, 165 (1970).
(22) F. D. Lewis and T. A. Hilliard, *J. Amer. Chem. Soc.*, **94**, 3852 (1972).
(23) F. D. Lewis and J. G. Magyar, *J. Org. Chem.*, **37**, 2102 (1972).
(24) F. D. Lewis and J. G. Magyar, *J. Amer. Chem. Soc.*, **95**, 5973 (1973).
(25) Bibenzyl quantum yields are corrected for the requirement of two photons per molecule of product.
(26) (a) P. J. Wagner, *J. Amer. Chem. Soc.*, **89**, 2820 (1967); (b) P. J. Wagner, J. M. McGrath, and R. G. Zepp, *ibid.*, **94**, 6883 (1972).
(27) S. G. Cohen and B. Green, *J. Amer. Chem. Soc.*, **91**, 6824 (1969).
(28) F. D. Lewis, *J. Phys. Chem.*, **74**, 3332 (1970).
(29) A. Heller and E. Wasserman, *J. Chem. Phys.*, **42**, 949 (1965).
(30) A. A. Lamola and G. S. Hammond, *J. Chem. Phys.*, **43**, 2129 (1965).
(31) W. D. K. Clark, A. D. Litt, and C. Steel, *J. Amer. Chem. Soc.*, **91**, 5413 (1969).
(32) L. Salem, W. G. Dauben, and N. J. Turro, *J. Chim. Phys.*, **70**, 694 (1973).
(33) P. D. Bartlett and N. A. Porter, *J. Amer. Chem. Soc.*, **90**, 5317 (1968).
(34) R. D. Burkhart, *J. Amer. Chem. Soc.*, **90**, 273 (1968).
(35) S. F. Nelsen and P. D. Bartlett, *J. Amer. Chem. Soc.*, **88**, 137 (1966).
(36) P. J. Wagner and J. M. McGrath, *J. Amer. Chem. Soc.*, **94**, 3849 (1972).
(37) R. M. Kellog in "Methods in Free Radical Chemistry," Vol. 2, E. S. Huyser, Ed., Marcel Dekker, New York, N. Y., 1969, Chapter 1.
(38) K. E. J. Barrett and W. A. Waters, *Discuss. Faraday Soc.*, **No. 14**, 221 (1953).
(39) R. G. Zepp and P. J. Wagner, *J. Chem. Soc., Chem. Commun.*, 167 (1972).
(40) S. A. Weiner and G. S. Hammond, *J. Amer. Chem. Soc.*, **91**, 986 (1969).
(41) N. J. Turro, J. C. Dalton, K. Dawes, G. Farrington, R. Hautala, D. Morton, M. Niemczyk, and N. Shore, *Accounts Chem. Res.*, **5**, 92 (1972).
(42) R. C. Cookson and N. S. Wariyar, *J. Chem. Soc.*, 2302 (1956).
(43) M. E. Scanlan and S. MacKenzie, *J. Org. Chem.*, **37**, 1579 (1972).
(44) P. J. Wagner, M. J. May, A. Haug, and D. R. Graber, *J. Amer. Chem. Soc.*, **92**, 5269 (1970), and references therein.
(45) (a) J. C. Dalton and N. J. Turro, *Ann. Rev. Phys. Chem.*, **21**, 499 (1970); (b) P. J. Wagner and R. W. Spoerke, *J. Amer. Chem. Soc.*, **91**, 4437 (1969); (c) O. L. Chapman and D. S. Weiss, *Org. Photochem.*, **3**, 197 (1973); (d) H. Paul and H. Fisher, *Helv. Chim. Acta*, **56**, 1575 (1973).
(46) G. S. Hammond, *J. Amer. Chem. Soc.*, **77**, 334 (1955).
(47) C. Walling and A. Padwa, *J. Amer. Chem. Soc.*, **85**, 1593 (1963).
(48) (a) C. Rüchardt, *Fortschv. Chem. Forsch.*, **6**, 251 (1966); (b) C. Rüchardt, *Angew. Chem., Int. Ed. Engl.*, **9**, 830 (1970); (c) C. Rüchardt, H.-D. Beckhaus, J. Bonnekessel, H. Bock, E. Dempewolf, F. A. Groeger, V. Golzke, G. Hamprecht, K. Herwig, J. Hinz, P. Lorenz, I. Mayer-Ruthardt, J. Müller, A. Oberlinner, and E. Schacht, XXIII International Congress of Pure and Applied Chemistry, Special Lectures, Vol. 4, Butterworths, London, 1971, p 223.
(49) The quantum yield for the formation of benzaldehyde from isobutyrophenone in 3×10^{-3} *M* RSH-benzene is 0.006. Thus unlike ketones **1**–**4** and **7**, its lifetime is primarily determined by the rate of radiationless decay and not the rate of α cleavage.
(50) F. D. Lewis and R. W. Johnson, *J. Amer. Chem. Soc.*, **94**, 8914 (1972).
(51) (a) N. C. Yang and R. L. Dusenbery, *J. Amer. Chem. Soc.*, **90**, 5899 (1968); (b) N. C. Yang and R. L. Dusenbery, *Mol. Photochem.*, **1**, 159 (1969).
(52) Possible explanations for the nonlinearity of such plots include competitive absorption by a strongly absorbing intermediate[27] and a solvent effect on the reactivity of the lowest triplet state.[28]
(53) k_α values for **1**–**4** given in our preliminary communication[9] were obtained before we made these observations.
(54) Competitive absorption by products cannot account for the decrease in quantum yield as the absorbance at 313 nm does not increase at <5% conversion. Benzaldehyde (E_T = 72 kcal/mol) is the only product with low enough triplet energy which is present in high enough concentration to be responsible for product quenching.
(55) (a) K. R. Huffman, C. E. Kuhn, and A. Zweig, *J. Amer. Chem. Soc.*, **92**, 599 (1970); (b) P. J. Wagner, I. E. Kochevar, and A. E. Kemppainen, *ibid.*, **94**, 7489 (1972).
(56) V. Meyer and L. Oelkers, *Ber.*, **21**, 1295 (1888).
(57) A. Brodhag and C. R. Hauser, *J. Amer. Chem. Soc.*, **77**, 3024 (1955).
(58) C. F. Koelsch, *J. Amer. Chem. Soc.*, **54**, 2049 (1932).
(59) R. Stierlin, *Ber.*, **22**, 376 (1889).
(60) H. Strassmann, *Ber.*, **22**, 1229 (1889).
(61) W. M. Moore and M. Ketchum, *J. Amer. Chem. Soc.*, **84**, 1368 (1962).
(62) C. G. Hatchard and C. A. Parker, *Proc. Roy. Soc., Ser. A*, **235**, 518 (1965).

Alumina-Catalyzed Reactions of Hydroxyarenes and Hydroaromatic Ketones. VII. Reaction of 5-Indanol with Methanol[1a]

LeRoy H. Klemm,* Reinhard Zell,[1b] and Joseph S. Shabtai[1c]

Department of Chemistry, University of Oregon, Eugene, Oregon 97403

Received July 3, 1973

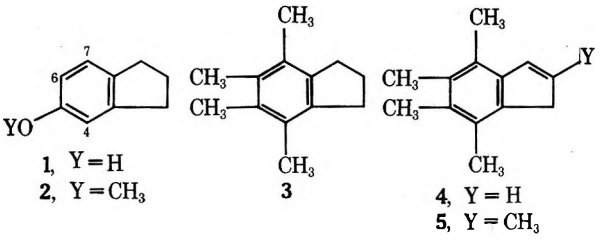
The alumina-catalyzed reaction of 5-indanol (1) with excess methanol was investigated as a function of temperature (330–520°) and catalyst acidity. 4,5,6,7-Tetramethylindan (3), 4,5,6,7-tetramethylindene (4), and 2,4,5,6,7-pentamethylindene (5) are the major products formed at 390–520° over a catalyst (B) containing sodium ion. Compound 4 is the main component (37–50 mol % yield, based on converted 1) at 390–420°, whereas 3 is favored (44–54 mol %) at 470–520°. At 470°, methanol serves as a hydrogen donor (for the forward reaction) in the quasi-equilibrium system 4 + 2H $\rightleftarrows$ 3. With a sodium-free catalyst (A), 3 is the main product from 1 at 390–420° (61 mol %), whereas 4 is a minor component. With A, the yield of 5 decreases (from 27 to 13 mol %) with increasing temperature in the range of 330–390°. Compound 5 was also synthesized by a noncatalytic method.

It was shown previously[2-4] that phenol and naphthols react with methanol at 400–550° in the presence of alumina catalysts to form polymethylarenes. At milder temperatures the formation of oxygen-containing intermediates, *i.e.*, methylated hydroxyarenes and hydroaromatic ketones, was observed. As an extension of these studies the alumina-catalyzed reaction of 5-indanol (1) with methanol, and its dependence on temperature (330–520°) and

catalyst acidity, was investigated. Since 1 is a substituted phenol, facile methylation of the aromatic ring was anticipated above 300°.

The experimental and analytical procedures were similar to those employed previously.[2-4] Catalysts used were A (sodium free alumina, obtained by hydrolysis of aluminum isopropoxide) and B (Harshaw alumina containing *ca.* 0.4% of sodium ion).[5] The molar ratio of methanol to 1 was 20:1 in all runs. Experimental data are summarized in Tables I and II.

As noted in Table I, there are three main products formed by reaction of 1 with methanol at 390–520° in the presence of B, or at 330–470° in the presence of A, *viz.*, 4,5,6,7-tetramethylindan (3), 4,5,6,7-tetramethylindene (4), and 2,4,5,6,7-pentamethylindene (5). In addition, 5-



1, Y = H
2, Y = CH_3

3

4, Y = H
5, Y = CH_3

methoxyindan (2) is produced with B below 400° and the yield of 2 increases as the temperature decreases toward 355°. The relative yields of 3 and 4 vary to a considerable extent with temperature and with catalyst acidity. With B, formation of 3 increases monotonously with increase of temperature from 355° (2 mol %) to 520° (54 mol %), whereas the yield of 4 reaches a maximum (*ca.* 50 mol %) near 420°. The yield of 4 is higher than that of 3 at 355–420°, while 3 is the major product at 470–520°. With A, on the other hand, 3 is the predominant component at all temperatures studied, while 4 is formed as a minor component only (expt 8–12). The maximum yield of 3 obtained with catalyst A is *ca.* 61 mol % at 420° (expt 11). Increase of temperature to 470° (expt 12) causes considerable decrease in the yield of 3, as a result of fragmentation reactions which lead to products of low molecular weight. With catalyst B the yield of pentamethylindene 5 reaches a maximum at *ca.* 390° (21 mol %, based on converted 1) and then remains nearly constant (at 9–13 mol %) in the range of 405–520°. With A the formation of 5 decreases with increasing temperature in the range of 330–420° (expt 8–11) and is 27 mol % (based on converted 1) at 330°. Altogether, for B at temperatures above 390° and for A at temperatures above 330° the average number of methyl groups per indene or indan ring present in the total identified product is close to 4.2.

Table II and Figure 1 show the results of a series of experiments in which a product mixture (from expt 13) was recycled five times (expt 14–18) through catalyst B at a constant temperature of 470°. A fresh portion of methanol was added to the recycled material in each run. The data show that the concentration of 3 increases with increasing reaction time and ultimately reaches a constant value of *ca.* 69 mol %, while the concentration of 4 consistently decreases to *ca.* 9 mol % (*i.e.*, the molar ratio of 3:4 of 7.7 is attained). Similarly, when one uses pure 3 as the starting material in recyclization experiments (expt 19–20) a molar ratio of 3:4 of 9.6 is attained. Extrapolation of these data (Figure 1, broken lines) to longer reaction times indicates that a convergent molar ratio of *ca.* 9.0 would result, corresponding to a pseudo-equilibrium relationship of 4 + 2H $\rightleftarrows$ 3, where the hydrogen is ultimately furnished by methanol. In contrast, the concentration of pentamethylindene 5 does not seem to be significantly altered by change in reaction time. A single recycle of the product mixture

Table I

Alumina-Catalyzed Reactions of 5-Indanol (1) with Methanol[a]

Experiment no.	1	2	3	4	5	6	7	8	9	10	11	12
Catalyst[b]	B	B	B	B	B	B	B	A	A	A	A	A
Reaction temp, °C	355	390	405	420	470	500	520	330	355	390	420	470
Conversion of 1, mol %	39	82	100	100	100	100	100	67	75	84	100	100
Product component,[c] mol %												
5-Methoxyindan (2)	15.8	10.2										
4,5,6,7-Tetramethylindan (3)	1.6	21.7	29.7	33.1	44.2	47.6	53.5	30.2	42.4	50.7	61.0	31.7
4,5,6,7-Tetramethylindene (4)	5.3	30.0	41.7	49.6	38.9	33.0	26.4	7.5	5.5	6.5	5.6	4.5
2,4,5,6,7-Pentamethylindene (5)	1.8	17.1	12.9	9.0	10.2	12.8	11.0	18.0	15.9	11.2	5.6	7.6
Unidentified[d]	13.9	2.9	13.6	13.0	10.6	9.1	13.0	11.6	12.5	16.5	19.4	39.8[e]
Depth of ring methylation[f]	1.5	2.9	4.1	4.1	4.1	4.1	4.1	4.3	4.2	4.2	4.1	4.2

[a] In each experiment a mixture of 6.7 g (0.05 mol) of 1, 32 g (1 mol) of methanol, and 10 ml of benzene was introduced into the reactor at a uniform rate over a period of 2 hr. [b] Forty grams of fresh catalyst was used in each experiment. [c] Calculated on the basis of 100 mol of starting 1 (including unreacted material). [d] Percentage by weight of total product; includes unidentified chromatographic peaks and nondistillable residues. [e] Mostly components of low molecular weight. [f] In average number of methyl groups per indan or indene moiety for all identified products (exclusive of recovered 1).

Table II
Alumina-Catalyzed Transformations in the Polymethylindan–Indene System with Methanol[a]

Experiment no.	13[b]	14[b]	15[b]	16[b]	17[b]	18[b]	19[c]	20[c]
Reaction time, hr[d]	0	2	4	6	8	10	6	12
Product component, mol %								
4,5,6,7-Tetramethylindan (3)	31.3	40.3	55.3	63.4	67.6	69.2	84.5	70.0
4,5,6,7-Tetramethylindene (4)	46.9	36.9	20.8	13.4	9.3	9.0	7.8	7.3
2,4,5,6,7-Pentamethylindene (5)	9.7	10.4	11.4	10.4	9.6	7.5		3.4
Unidentified[e]	12.1	12.4	12.5	12.8	13.5	14.3	7.7	12.3

[a] Reaction temperature, 470°; catalyst B. [b] Experiments 13–18 were run consecutively by recycling 6 g of a mixture of initial composition indicated under expt 13 (zero reaction time) with a fresh portion of methanol (32 g) and benzene (10 ml) for each run. [c] Experiments 19 and 20 were run by recycling pure 3 (0.5 g) with fresh methanol (16 g) and benzene (4 ml). [d] Cumulated reaction time. [e] See footnote *d*, Table I.

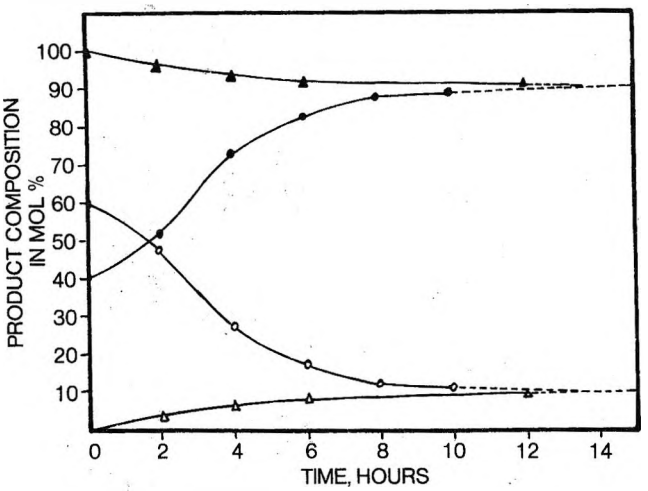
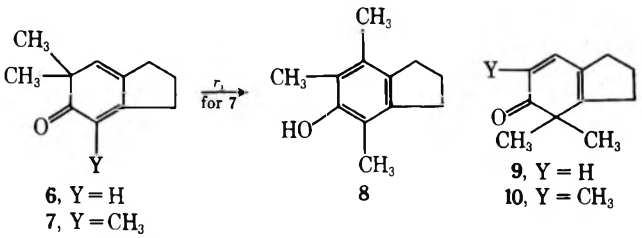


Figure 1. Interconversion of 4,5,6,7-tetramethylindan (3) and 4,5,6,7-tetramethylindene (4) at 470° in the presence of catalyst B and excess methanol, as a function of total reaction time. Starting materials: (a) a mixture (3:2, mol/mol) of 4 (open circles) and 3 (solid circles); (b) pure 3 (solid triangles), without 4 (open triangles).

from expt 13 through B at 420° showed no appreciable interconversion of 3 and 4.

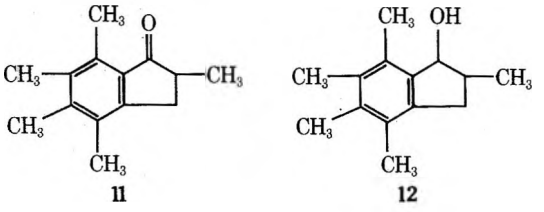
In analogy to the reactions of phenol and naphthols[2-4] with methanol in the presence of alumina, it is presumed that production of hydrocarbons 3–5 is preceded by the formation of C-methylated oxygen-bearing precursors. No attempt was made to isolate these intermediates in the indanol system. However, it seems likely that direct C-methylation of the aromatic ring in 1 will occur by electrophilic attack at C-4 and C-6 only, while methylation at C-5 and C-7 results from migration of ortho methyl substituents in the manner proposed earlier. Thus, in the previously presented shorthand notation for possible sequential pathways in the 1-naphthol series,[2c] one can derive 3 from 1 by any of the following alternative routes (listed in order of increasing energy of an intermediate): (6,4,6),*r*,6,*Rr*, (6,4,6),*r*,4,*Rr*, 6,6,*r*,4,4,*Rr*, 7a,*r*,(6,4,6),*Rr*, and 7a,*r*,(6,4,4),*Rr*, where the numbers refer to successive positions of ring methylation, parenthesized numbers represent allowed permutations in the methylation sequence, *r* symbolizes the dienone–phenol rearrangement (as in the transformation 7 → 8), and *Rr* indicates the terminal reduction–rearrangement process. If dimethylation occurred at C-4 more readily than at C-6 under the conditions used, one should have found appreciable amounts of 4,5-dimethylindan and 4,5,6-trimethylindan (formed *via* intermediates **9** and **10**, respectively) among the isolable products. The difference in facility toward dimethylation at these two positions may be ascribed to the fact that each of the molecules **9** and **10** contains a high-energy eclipsed (by the hydrogen atoms at C-3) geminal dimethyl group, while the isomeric compound **6** or **7**, respectively, does not.



6, Y = H
7, Y = CH_3
8
9, Y = H
10, Y = CH_3

Experiments 13–20 show that the rate of conversion of **3** and **4** into pentamethylindene **5** is slow in comparison to the rate of conversion of 5-indanol (**1**) into **5** (expt 5). It is suggested that in the transformation **1** → **5** dehydrogenation to an indenol plus methylation at C-2 precede the process of deoxygenation and that **8** is a likely intermediate along the reaction pathway.

The structure of **5** was confirmed by an independent synthesis starting with Friedel–Crafts alkylation of 1,2,3,4-tetramethylbenzene by means of methyl 3-bromoisobutyrate. Cyclization of the condensation product gave 2,4,5,6,7-pentamethyl-1-indanone (**11**), which was reduced to the carbinol **12** and dehydrated to **5**.



11 **12**

Experimental Section[6]

Procedure. Experiments 13–20 (Table II) were carried out in the apparatus described previously,[2a] while expt 1–12 (Table I) were conducted in a 60 × 2.2 cm (i.d.) stainless steel tube (isothermal zone 25 cm in length). Catalysts A and B were the same as used before and were activated at 600°.[5] In expt 1–12 the hot catalyst was washed with 10 ml of MeOH and then 100 ml of benzene after the reaction proper. Further processing was conducted as before, except that recovered acidic components were extracted into benzene and separations and identifications of reaction products were accomplished by vpc by means of a stationary phase of 10% Bentone 34 plus 5% DC-550 silicone fluid on 60–80 mesh Chromosorb W at 180°.

Isolation and Identification of Reaction Products. 5-Methoxyindan (2) [n^{25}D 1.5424; ir (CS_2) 1250 (Ar–O stretch) and 1070 cm^{-1} (CH_3–O stretch)[7]] was isolated from expt 2 and identified by *n*D and pmr.[8] 4,5,6,7-Tetramethylindan (**3**) [ir (CS_2) 2950 (s), 1380 (m), 1316 cm^{-1} (w); ir ($CHCl_3$) 1416 cm^{-1} (s)] and 4,5,6,7-tetramethylindene (**4**) [ir (CS_2) 2940 (s), 697 cm^{-1} (m, cis CH=CH); ir ($CHCl_3$) 1615 cm^{-1} (w, C=C stretch); uv max (95% EtOH) 218 nm (ε 17,200), 223 (16,700)] were isolated from reaction mixtures and identified by elemental analyses, as well as by comparison of melting points and pmr spectra with literature data.[9]

2,4,5,6,7-Pentamethylindene (5) was isolated from expt 3 and 8 and recrystallized from MeOH: mp 127–128° (picrate, dark red needles from EtOH, mp 145–146° dec); pmr (CCl_4) δ 2.08, 2.14, and 2.22 (3 overlapping s, 15, 5 CH_3), 3.05 (broadened s, 2, CH_2 at C-1), 6.52 (m, 1, H-3); pmr ($CDCl_3$) δ 2.13, 2.23, and 2.30 (3 s,

15), 3.19 (broadened s, 2), 6.60 (m, 1); ir (CS_2) 1395 (m), 905 (m), 828 cm^{-1} (m); ir ($CHCl_3$) 2950 (s), 1620 (m, C=C stretching), 1451 cm^{-1} (s); uv max (95% EtOH) 220 nm (ϵ 20,900), 225 (21,700).

Anal. Calcd for $C_{14}H_{18}$: C, 90.26; H, 9.74. Found: C, 90.15; H, 9.82.

Isolated and synthetic samples (*vide infra*) of **5** were identical.

Syntheses of Reference Compounds. 2,4,5,6,7-Pentamethyl-1-indanone (11).[10] A mixture of 11.5 g (0.086 mol) of 1,2,3,4-tetramethylbenzene, 15 g (0.083 mol) of methyl 3-bromoisobutyrate,[11] and 50 g of anhydrous $AlCl_3$ was maintained at 135° until evolution of hydrogen halide gas ceased (2 hr). The reaction mixture was treated with ice–water and extracted with benzene. Evaporation of the extract left a solid which was recrystallized from MeOH and then stirred and heated (steam bath) with 125 ml of concentrated H_2SO_4 for 14 hr. The mixture was poured into ice–water and extracted with benzene. Evaporation gave a crude solid which was purified by repetitive evaporative distillation at 130° (0.5 mm) to give 3.7 g (22%) of **11**, mp 72–76°, converted to needles (mp 85–86°) on recrystallization from MeOH: pmr ($CDCl_3$) δ 1.31 (d, 3, J = 7.3 Hz, CH_3 at C-2), 2.64 (s, 3, CH_3 at C-7) superimposed on 1.8–3.5 (m, 12, H-2, 2 H-3, 3 CH_3);[12] ir (CS_2) 2980, 2950, 1705 (C=O),[13] 1328, 1282, 1148 cm^{-1}; ir ($CHCl_3$) 1587, 1462, 1385 cm^{-1}.

Anal. Calcd for $C_{14}H_{18}O$: C, 83.12; H, 8.97. Found: C, 82.99; H, 9.04.

2,4,5,6,7-Pentamethyl-1-indanol (12). To a stirred, cold (0°) suspension of 0.5 g of $LiAlH_4$ in 90 ml of ether was added dropwise a solution of 2 g of **11** in 10 ml of ether. After further stirring (2 hr), the cold mixture was treated with aqueous NH_4Cl and extracted with ether. Evaporation of solvent and recrystallization of the residue from MeOH gave 0.7 g (35%) of **12** as white prisms: mp 130–131°; pmr (CCl_4) δ 1.02 (d, 3, J = 7 Hz, CH_3 at C-2), 1.5–3.4 (m, 16, H-1, H-2, 2 H-3, 4 CH_3),[14] 4.6 (broad signal, 1, OH); ir (CS_2) 2970, 2940 cm^{-1}; ir ($CHCl_3$) 3625 (OH), 1464, 1387 cm^{-1}.

Anal. Calcd for $C_{14}H_{20}O$: C, 82.30; H, 9.87. Found: C, 82.03; H, 9.58.

2,4,5,6,7-Pentamethylindene (5). An intimate mixture of 0.3 g of carbinol **12** and 3 g of alumina was heated at 150° (1 atm) for 2 hr and then evaporatively distilled (150°, 0.6 mm) to give 0.14 g (51%) of crystalline **5**. Recrystallization from MeOH gave a sample which was identical with that isolated from catalytic reaction (*vide supra*).

Acknowledgment. One of us (R. Z.) wishes to thank the West German government for the award of a NATO Postdoctoral Fellowship, which made this study possible.

Registry No.—**1**, 1470-94-6; **2**, 5111-69-3; **3**, 707-95-9; **4**, 707-96-0; **5**, 50415-46-8; **5** picrate, 50415-47-9; **11**, 50415-48-0; **12**, 50415-49-1; methanol, 67-56-1; 1,2,3,4-tetramethylbenzene, 488-23-3; methyl 3-bromoisobutyrate, 20609-71-6.

References and Notes

(1) (a) This investigation was supported by Research Grant No. CA-5969 from the National Cancer Institute, U. S. Public Health Service. (b) NATO Postdoctoral Fellow, 1966–1967. (c) On leave from the Department of Chemistry, Weizmann Institute of Science, Rehovoth, Israel, 1964–1969.
(2) (a) L. H. Klemm, J. Shabtai, and D. R. Taylor, *J. Org. Chem.*, **33**, 1480 (1968); (b) *ibid.*, **33**, 1489 (1968); (c) *ibid.*, **33**, 1494 (1968); (d) *ibid.*, **35**, 1075 (1970).
(3) L. H. Klemm, J. Shabtai, and C. E. Klopfenstein, *J. Org. Chem.*, **35**, 1069 (1970).
(4) L. H. Klemm and D. R. Taylor, *J. Org. Chem.*, **35**, 3216 (1970).
(5) For simplicity, catalysts are designated by the same capital letters, respectively, as used in earlier papers.[2,3] For determination of acidities of these catalysts see ref 2a and papers cited therein.
(6) Elemental analyses were performed by Micro-Tech Laboratories, Skokie, Ill. Infrared spectra were obtained by means of a Beckman IR-7 spectrometer; pmr spectra by means of a Varian Associates A-60 instrument, with tetramethylsilane as internal reference; and ultraviolet spectra by means of a Cary 15 spectrophotometer.
(7) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd ed, Methuen London, 1958, pp 116–117.
(8) H. O. House and C. J. Blankley, *J. Org. Chem.*, **33**, 53 (1968).
(9) R. Criegee, F. Forg, H. A. Brune, and D. Schonleber, *Chem. Ber.*, **97**, 3461 (1964).
(10) This synthesis followed a general procedure given in ref 9.
(11) G. R. Clemo and T. A. Melrose, *J. Chem. Soc.*, 424 (1942).
(12) The methyl signals occur as overlapping singlets in the region δ 2.2–2.3.
(13) *Cf.* values of 1705–1710 cm^{-1} for indanone and methyl-substituted indanones: "Sadtler Standard Infrared Spectra Catalog," Spectra No. 3426, 4890, 14324.
(14) The methyl signals occur as overlapping singlets in the region δ 2.1–2.3.

Noble Metal Catalysis. III. Preparation of Dialkyl Oxalates by Oxidative Carbonylation

Donald M. Fenton* and Paul J. Steinwand

Union Research Center, Brea, California 92621

Received May 22, 1973

Dialkyl oxalates can be prepared in good yields by oxidative carbonylation in the presence of alcohols and dehydrating agents using a palladium redox system and oxygen. The other product, water, is removed by the dehydrating agent. If the dehydrating agent is not effective, then large amounts of carbon dioxide are made and no oxalates are found. At low carbon monoxide pressure increased amounts of dialkyl carbonate are also found. Of the various cocatalysts tried, a cupric chloride–cuprous chloride system was found to be the most selective.

Dialkyl oxalates can be prepared in good yields by oxidative carbonylation[1] in the presence of alcohol and dehydrating agents using a palladium redox system according to eq 1 and 2.

$$2CO + 2ROH + \tfrac{1}{2}O_2 \longrightarrow RO_2CCO_2R + H_2O \quad (1)$$

$$H_2O + (RO)_2CH \longrightarrow 2ROH + HCO_2R \quad (2)$$

The dehydrating agent is necessary; otherwise large amounts of carbon dioxide are produced and no oxalates are found. The palladium redox system is somewhat similar to the one used in acetaldehyde synthesis,[2] but optimum results are achieved by restricting the amounts of chloride ion. In addition, carbonates are produced by much the same chemistry.

Results

The major products of the reaction are oxalates and carbonates, but, in addition, there are also produced under some conditions significant amounts of carbon dioxide and esters arising from solvent attack. Under acidic conditions some alkyl halides and ethers are also produced. Table I shows some of the results concerning the synthesis of diethyl oxalate using two of the three useful cocatalysts, iron and copper halides. An example of the third cocatalyst type, the quinones, is shown in the Experimental Section.

A comparison of runs 1 and 3 shows that although ferric chloride gives much the better ratio of oxalate to carbonate than does cupric chloride, ferric chloride causes the

Table I
Synthesis of Diethyl Oxalate

Run	Cocatalyst[a]	Millimoles of cocatalyst	Initial pressure of carbon monoxide, psig	Mol % yield, carbonate plus oxalate to total yield	Mole ratio: Oxalate to carbonate	Mole ratio: Oxalate plus carbonate to CO_2	Mole ratio: Oxalate plus carbonate to acetate
1	$FeCl_3$	62	1000	31	2.5	5.7	0.49
2	$FeCl_3$	62	1000	23	0.27	0.40	1.1
	LiCl	71					
3	$CuCl_2$	37	1000	81	1.4	5.6	18
4	$CuCl_2$	37	1000	31	0.44	2.3	0.57
	LiCl	118					
5	$CuCl_2$	36	500	72	0.14	5.0	5.3
	LiCl	118					
6	$FeCl_2$	47	1000	35[c]	2.6		0.55
	HCl	28					
7	$FeCl_2$	62	1000	37	0.41	4.5	0.66
	LiCl	62					
8	$FeCl_3$	62	1000	30	1.4	1.2	0.64
	NaOAc	74					
9	$CuCl_2$	35	1000	92[c]	1.4		12
	$Cu(OAc)_2$	30					
10	$CuCl_2$	35	1000	93[c]	2.4		>40
	Cu_2Cl_2	50					
11	$FeCl_3$	22	1000	35[c]	0.53		0.54
	$PdCl_2$	17					
12[b]	$CuCl_2$	35	500		0.52		
	Cu_2Cl_2	30					
13[b]	$CuCl_2$	35	1000		1.3		
	Cu_2Cl_2	30					

[a] With 6 mmol of $PdCl_2$ (except where noted), 200 ml of absolute ethanol, and 200 ml of triethyl orthoformate in a stirred 0.5-gal autoclave and oxygen addition in 10–20-psig increments until a total of 150–500 psig had been added, temperature 125°. [b] Using methanol and trimethyl orthoformate instead of ethanol and triethyl orthoformate. [c] Carbon dioxide yield not included.

production of large amounts of ethyl acetate. The production of ethyl acetate is quite severe for all of the iron runs and is consistent with the fact that the iron halides, independent of palladium, are known to oxidize ethanol to acetaldehyde and finally to ethyl acetate.[3] The effect of additional chloride can be seen in runs 2 and 4. The addition of chloride decreases the ratio of oxalate to carbonate for both iron and copper and decreases the ratio of oxalate plus carbonate to carbon dioxide. Also the attack on solvent in run 4 is severe. The effect of acids and bases can be seen in runs 6–9. Run 6 might be expected to give similar results to run 1 as long as the oxidation of $FeCl_2$ is reasonably complete, according to eq 3, and such was found

$$2FeCl_2 + 2HCl + \tfrac{1}{2}O_2 \longrightarrow 2FeCl_3 + H_2O \quad (3)$$

to be the case. In run 7 the effect of base is seen. To the extent that eq 3 proceeds to the right then in this case an equivalent of base is produced. Since the results of this experiment are not as satisfactory as compared to run 1, then the presence of base must be deleterious. This is further seen in run 8, where NaOAc (which is not as strong a base as lithium ethoxide) also brings the oxalate to carbonate ratio down. The presence of copper acetate in run 9 creates two effects. It removes excess chloride, which is indicated in run 10 to be highly beneficial, but it also increases the amount of base which is detrimental. Run 10 shows that the addition of cuprous chloride is highly beneficial. No attack on solvent was discernible. The actual concentration of cuprous chloride is unknown, since cuprous chloride is somewhat insoluble. Run 11 shows that most of the palladium is not in the oxidized form because the liberated chloride makes run 11 more like run 2 rather than like run 1.

Table I shows the effects of increasing the carbon monoxide pressure from 500 to 1000 psig (runs 4, 5, 12, 13). In both sets there is a significant increase in the oxalate–carbonate ratio. On the other hand, an increase in the pressure of carbon monoxide leads to higher rates of production of carbon dioxide and ethyl acetate.

If oxygen is not used then water is not formed and it is not necessary to use dehydrating agents. Such is the case where benzoquinone alone is used as the oxidant, as shown in the Experimental Section, although orthoformates are beneficial.

Discussion

Although the equations for the regeneration reactions for the catalyst system[4] are frequently described (for copper) as in eq 4 and 5, it may be that these reactions do

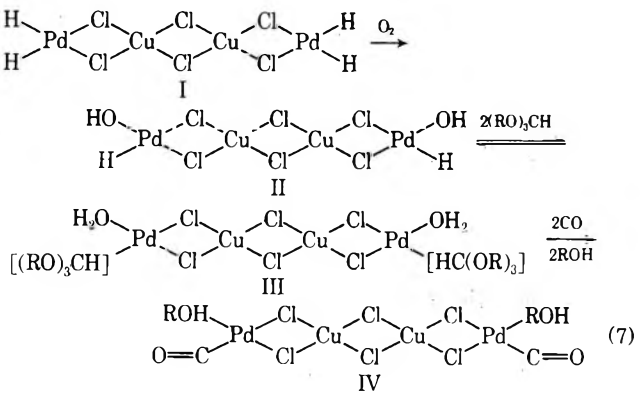
$$Pd^0 + 2CuCl_2 \longrightarrow Cu_2Cl_2 + PdCl_2 \quad (4)$$

$$Cu_2Cl_2 + 2HCl + \tfrac{1}{2}O_2 \longrightarrow 2CuCl_2 + H_2O \quad (5)$$

not occur in discrete steps. If the reactions were discrete steps, then the liberation of water according to eq 5 would occur independently of palladium so that at least some of the time palladium(II) might be expected to react as if no water was present. However, it was already seen that orthoformates are necessary for oxalate production, though even in the presence of orthoformates some carbon dioxide is obtained. It was therefore concluded that the water molecule is an important ligand coordinated to palladium. This conclusion is consistent with the fact that water was shown to have a pronounced influence in the oxidation of olefins to succinates[5] as illustrated in eq 6.

$$2ROH + 2CO + \text{>C=C<} + \tfrac{1}{2}O_2 \longrightarrow RO_2C\text{—}C\text{—}C\text{—}CO_2R + H_2O \quad (6)$$

Since either iron or copper halides or quinones are necessary for sustained reaction, it is concluded that these materials complex to palladium. Therefore the following complex, I, is postulated as the reduced species (for copper) and the following reactions illustrate its oxidation.



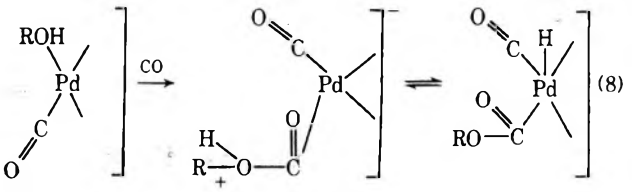
(7)

The oxygen atoms can be transferred by epoxide-type bridges between metal atoms or possibly by hypohalite exchanges, although hypohalite-type oxidation products are found only when quite high concentrations of copper are used.[6] The need for two palladium atoms in complex I is deduced from the fact that if only one was present, then two molecules of water (from O_2) would eventually come from a single palladium, which demands that the second palladium would not have an initial water ligand, so that some oxalate and carbonate should be formed in the absence of dehydrating agent. Two cuprous chlorides are used because in that way the addition or subtraction of halide ion as the complexes are oxidized and reduced is not necessary. It is postulated that there is an equilibrium between complexes having water in its dissociated form, II, and water in its undissociated form, III. It is proposed that the next advantageous step is the removal of the water ligand from the palladium. If this water is not removed then carbon dioxide is a likely product. Since the trialkyl orthoformate, under the conditions listed in Table I, is the only agent capable of water removal, then other ligands which compete favorably with the orthoformate should be kept to minimums. From Table I, it is seen that excess chloride ion increases the fraction of carbon dioxide synthesis. Also, from Table I, it can be seen that while increasing the carbon monoxide pressure from 500 to 1000 psig increased the oxalate to carbonate ratio it also increases the fraction of carbon dioxide made. Therefore carbon monoxide also impedes the formation of palladium–orthoformate bonds.

The orthoformate ligand can then react with the water ligand to give alcohol and alkyl formate. The question then arises as to whether it is the oxidation of two alkyl formates to dialkyl oxalates that is occurring instead of, or in addition to, the oxidation of carbon monoxide to oxalates. To answer this question methyl formate with trimethyl orthoformate was heated with palladium chloride using benzoquinone as a cooxidant in a closed system. Neither carbonate nor oxalate was found. In addition benzyl formate under oxidizing conditions in an open system was not consumed and benzoquinone was recovered unreacted. Also neither tributyl orthoformate nor trimethyl orthoformate gave carbonates or oxalates under oxidizing conditions.

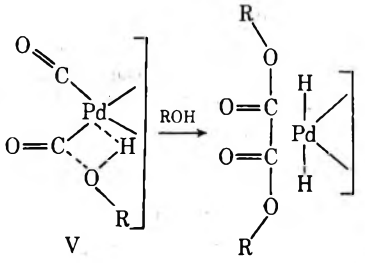
It is seen from Table I that cuprous chloride is highly beneficial and that most of the palladium is not in the Pd(II) oxidation state. All of these facts are consistent with the proposal that I is the main form of the redox system during oxalate synthesis. The same type of a complex can be written for ferrous chloride in place of cuprous if the additional two chlorides are both placed on the same side of the otherwise planar ring systems. The oxygen can then migrate on the opposite side.

Proposed Mechanism of Oxalate Formation. Several palladium carbonyl complexes are known, including one containing two coordinated carbonyl ligands. Also palladium carboalkoxyl complexes are known.[7] Starting with complex IV it is envisioned that a carboalkoxyl ligand is formed, according to eq 8.



(8)

Any negative charge generated on palladium can also be expected to be stabilized by the attached copper ligands through the chloride bridges to the copper atoms. It is also possible that the hydrogen may occupy an intermediate site, *e.g.*, V. The attack of another alcohol molecule then triggers the production of oxalates.



(9)

Experimental Section

The reactions were carried out in either stainless steel or titanium autoclaves. The steel autoclaves sometimes exhibited excessive corrosion, particularly when excess halide ion was used. However, corrosion was much reduced when halide acceptors were used, such as cuprous chloride. Titanium parts are not advised since under anhydrous conditions with oxygen, titanium was shown to react, sometimes explosively, particularly in the oxygen inlet line, to give, at least in some cases, titanium tetraalkoxides. Teflon parts were found to be highly advantageous. The catalyst system and liquids were charged to the autoclave and carbon monoxide was added to the desired pressure. Stirring was commenced and the autoclave was heated to the desired temperature. Oxygen was then added (controlled from behind a suitable barricade) in 10–20-psig increments. In almost all cases an immediate exotherm was noted and cooling water was circulated to bring the temperature under control. Pressure drops were noted. Oxygen was added until 150–500 psig had been added or until the reaction slowed down. In those cases where no noticeable reaction occurred, no more than 40 psig oxygen was added. After oxygen addition the autoclave was cooled to room temperature and the gases were collected and analyzed by gas chromatography. The liquid was weighed and analyzed by gas chromatography and occasionally by distillation.

Oxalate Synthesis Using Benzoquinone as Sole Oxidant. A. With Triethyl Orthoformate. To 30 g of benzoquinone, 0.5 g of palladium chloride, 100 ml of ethanol, and 20 ml of triethyl orthoformate in a 300-ml capacity titanium bomb was added carbon monoxide to 1000 psig. The mixture was rocked and heated to 125° for 4 hr. The final pressure was 500 psig. The liquid product (94 g) contained 8.4 wt % ethyl carbonate and 1.49 wt % ethyl oxalate, or a mole ratio of oxalate to carbonate of 1.4.

B. With Triethyl Orthoacetate. To 20 g of benzoquinone, 0.5 g of palladium chloride, 70 ml of anhydrous ethanol, and 30 ml of triethyl orthoacetate in a 300-ml capacity stainless steel bomb was added carbon monoxide to 800 psig. The mixture was rocked and heated to 125° for 4 hr. The liquid product (75 g) contained 0.5 wt % diethyl carbonate and 1.9 wt % diethyl oxalate. No ethyl formate was noted.

C. No Drying Agent. To 20 g of benzoquinone, 70 ml of anhydrous ethanol, and 0.5 g of palladium chloride in a 300-ml capacity stainless steel bomb was added carbon monoxide to 800 psig. The mixture was rocked and heated to 125° for 4 hr. The liquid product (55 g) contained 1.1 wt % diethyl carbonate and 1.2 wt % diethyl oxalate. No ethyl formate was noted.

Registry No.—Diethyl oxalate, 95-92-1; $FeCl_3$, 7705-08-0; LiCl, 7447-41-8; $CuCl_2$, 7447-39-4; $FeCl_2$, 7758-94-3; HCl, 7647-01-0;

NaOAc, 127-09-3; $Cu(OAc)_2$, 142-71-2; Cu_2Cl_2, 12258-96-7; $PdCl_2$, 7647-10-1.

References and Notes

(1) D. M. Fenton and P. J. Steinwand, U. S. Patent 3,393,136 (1972); D. M. Fenton and K. L. Olivier, *Chem. Technol.*, 220 (1972).
(2) J. Smidt, *Angew. Chem.*, 176 (1959).
(3) J. R. Pound, *J. Phys. Chem.*, **43**, 955, 969 (1939).
(4) D. M. Maitlis, "The Organic Chemistry of Palladium, Catalytic Reactions." Vol. II, Academic Press, New York, N. Y., 1971, p 77.
(5) D. M. Fenton and P. J. Steinwand, *J. Org. Chem.*, 37, 2034 (1972).
(6) Reference 4, p 81; P. M. Henry, *J. Org. Chem.*, 32, 2575 (1967).
(7) E. W. Stern, *Catal. Rev.*, **1**, 73 (1967); A. Misono, Y. Uchida, M. Hidai, and K. Kudo, *J. Organometal Chem.*, **20**, 7 (1969); K. Kudo, M. Hidai, and Y. Uchida, *ibid.*, **33**, 393 (1971).

Conformational Analysis. XCIX. The 1-Decalone Ring System[1,2]

Norman L. Allinger,* Geoffrey A. Lane, and Grace L. Wang

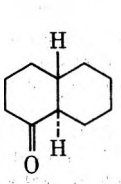
Departments of Chemistry, University of Georgia, Athens, Georgia 30602, and Wayne State University, Detroit, Michigan 48202

Received August 13, 1973.

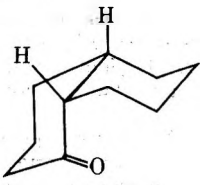
The equilibrium point for the isomerization of the 5α- and 5β-cholestan-4-ones has been redetermined to be 87 ± 1% 5α in ethanol at 25°, and earlier conflicting reports have been resolved. For the model 10-methyl-1-decalone system, the trans isomer is reported to be slightly favored at equilibrium, while, for the 9-methyl-1-decalone system, the cis isomer is favored. All of these results are well reproduced by a molecular mechanics calculation, and are discussed.

Twenty years ago Turner[3] was able to account quite well for the observed energy difference between *cis*- and *trans*-decalin, and to predict an energy difference between *cis*- and *trans*-9-methyldecalin (later verified experimentally[4,5]) in terms of the number of "gauche-butane"-like interactions in each isomer. The conformational analysis of decalone systems has presented a greater challenge, as numerous interactions between the carbonyl moiety and the rest of molecule have to be allowed for, including changes in the ring geometry due to the introduction of a carbonyl group. Early vector analysis calculations by Corey and Sneen[6] showed that these changes were likely to be important.

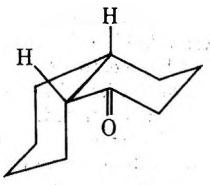
Klyne[7] sought to provide a systematic analysis of the interactions involved in decalone systems in terms of "alkyl ketone effects." His predictions concerning the conformational energies of 2-decalone systems have been borne out by experiments and recent force-field calculations.[8] In 1-decalone systems (**1**-**9**) he was able to account for the observed[9] stability of *trans*-1-decalone (**1**) as compared to *cis*-1-decalone (**2**, **3**), and for the excess[10] of *cis*- (**5**, **6**) over *trans*-9-methyl-1-decalone (**4**) at equilibrium. However, he calculated the *cis*-(a)-10-methyl-1-decalone conformer (**9**) to be of lower energy than *trans*-10-methyl-1-decalone (**7**), while the trans isomer is found experimentally to be the more stable. Since that time several equilibration studies have been carried out on 1-decalone systems[11-16] and steroidal analogs.[17-26] Conformational preferences have been deduced from ORD[27] and nmr[28] data, and these results have been discussed in terms of alkyl ketone effects.[29] Difficulties have persisted, particularly in reconciling the results reported for 1-decalone with those for steroidal analogs.



1

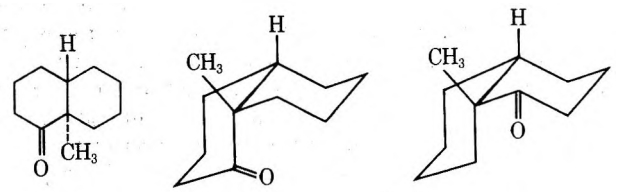


2

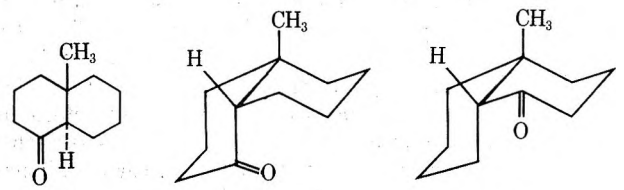


3

The advent of high-speed computers has permitted the application of molecular mechanics (or force-field) calculation methods to conformational problems. This approach explicitly allows for the relief of steric strain by distortion, and permits quantitative analysis of complex systems. In earlier papers in this series the method has been developed and applied to hydrocarbons,[30] ketones,[31,32] and other types of structures. The force field used for the present work differs only trivially from that described earlier.[32] An initial study of the 10-methyl-1-decalone system (**7**, **8**, **9**) by this method[31] showed that the observed $\Delta G°$ trans $\rightleftharpoons$ cis of ~0.2 kcal[14-16] could be accounted for.

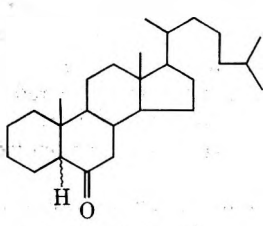


4 **5** **6**

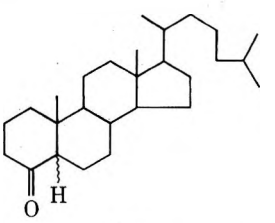


7 **8** **9**

In an earlier paper in this series[17] on the cis $\rightleftharpoons$ trans equilibria of cholestan-6-ones (**10**, **11**) and cholestan-4-ones (**12**, **13**), experimental free-energy differences of 1.2 and 2.1 kcal, respectively, were reported. These values stand in marked contrast to the small $\Delta G°$ found in the 10-methyl-1-decalone system (above), and the reported preponderance of the cis epimer of 9-methyl-1-decalone at equilibrium.[10] The cholestan-4-one equilibrium (**12**, **13**) can be considered to provide an experimental definition of



10, 5α
11, 5β



12, 5α
13, 5β

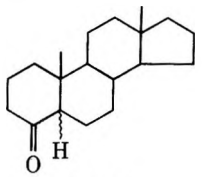
Table I
Heats and Free Energies of Isomerization (kcal/mol) for 1-Decalones[a]

Registry no.	Compd, conformer	$\Delta H°$ (trans ⇌ cis) Calcd	$\Delta H°$ (trans ⇌ cis) Exptl	$\Delta G°$ (trans ⇌ cis) Calcd	$\Delta G°$ (trans ⇌ cis) Exptl	Ref
493-02-7	*trans*-Decalin	0.0				
493-01-6	*cis*-Decalin	2.77	2.72 ± 0.20[c]			
21370-71-8	*trans*-1-Decalone (**1**)	0.0		0.0	0.0	38
32166-40-8	*cis*-1-Decalone (**2**)	1.97		1.85 (298)[h]	1.30[e]	12
	cis-1-Decalone (**3**)	2.87		1.77 (383)	1.15 (383)	13
				1.64 (493)	2.89 (493)	9
				1.61 (523)	2.30	
					3.10 (523)	11
2547-27-5	*trans*-9-Methyldecalin	0.0		0.0	0.0	
2547-26-4	*cis*-9-Methyldecalin	0.51	0.55 ± 0.28			5
			1.39 ± 0.64[f]			4
937-99-5	*trans*-9-Methyl-1-decalone (**4**)	0.0		0.0	0.0	
937-98-4	*cis*-9-Methyl-1-decalone (**5**)	0.13		−0.11 (298)		
	cis-9-Methyl-1-decalone (**6**)	0.53		−0.41 (523)	−0.37 (623)	10
937-77-9	*trans*-10-Methyl-1-decalone (**7**)	0.0		0.0	0.0	
770-62-7	*cis*-10-Methyl-1-decalone (**8**)	0.78[b]		0.42 (298)	0.21 (298)	15
	cis-10-Methyl-1-decalone (**9**)	0.89			0.21	
					0.10 (298)	14
				0.35 (350)	0.50 (350)	16
438-22-2	5α-Androstane	0.0				
438-23-3	5β-Androstane	0.84	0.89 ± 0.45			40
566-51-8	5α-Cholestan-4-one (**12**)	0.0		0.0	0.0	
6105-15-3	5β-Cholestan-4-one (**13**)	0.90[d]			1.10	
					1.20 (298)	
570-46-7	5α-Cholestan-6-one (**10**)	0.0		0.0	0.0	17, 24
13713-79-6	5β-Cholestan-6-one (**11**)	1.05[d]			1.16	
					1.25 (298)[g]	25
					1.12 (353)	24
					0.98	
					0.99 (373)	24
					1.05	
					1.08 (503)	24

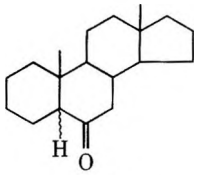
[a] In converting $\Delta H°$ figures to $\Delta G°$ terms symmetry numbers and optical activity effects are the same for all the bycyclic 1-decalone systesms (**1**–**9**). If a calculated $\Delta G°$ is not given, it is identical with the calculated $\Delta H°$ value. The calculated values for $\Delta H°$ are for individual conformations, while the $\Delta G°$ values are for the actual compounds, usually conformational mixtures. [b] *Cf.* 0.37 kcal (**8**), 0.70 kcal (**9**): ref 31. [c] A gas-phase $\Delta H°_{isom}$ of 3.17 kcal has been reported: ref 39. [d] Calculated values are for the androstanones (**14**–**17**). [e] Temperature not stated. [f] Heat of combustion data. [g] A $\Delta G°$ value of 1.06–1.13 is quoted for androstan-6-one in ref 25. [h] Temperature in °K.

an "*n*-butanal effect"[33] when compared to the hydrocarbon. In this case the 3-alkyl ketone and 2-alkyl ketone effects[7] are the same for the cis and trans isomers. The high value of $\Delta G°$ (trans ⇌ cis) found for cholestan-4-one was thus rationalized in terms of an *n*-butanal interaction of 0.88 kcal between the 4-ketone oxygen atom and the 7α hydrogen.[17] This figure was revised upward to 0.8–1.4 kcal/mol by Robinson.[33] Initial force-field calculations[31] on the *cis*-(e)-10-methyl-1-decalone (**8**) ("steroid" in the paper) structure failed to bear out this suggestion. The discrepancy between the equilibria of the steroid systems (**10**–**13**) and the 10-methyl-1-decalones (**7**–**9**), if 5β-cholestan-6-one (**11**) were taken to be a model for the low-energy cis conformer, has also remained to be accounted for.

Inspection of the literature since the reported equilibration of the cholestan-4-ones (**12**, **13**) to a mixture containing over 99% of the trans isomer reveals two reports at variance with this. Gutzwiller and Djerassi[18] report an equilibrium mixture containing ~90% of the trans isomer for the androstan-4-ones (**14**, **15**). Although large effects on the cis–trans equilibrium due to changes in the 17 substituent have been reported for ring A hydroxy-6-keto steroids,[26] in the absence of oxygen functionality in the side chain in either case it seemed unlikely[25] that this could account for the discrepancy. More recently, Robinson and Milewich[19] reported that an equilibration of cholestan-4-ones in refluxing methanol gave a mixture of 83% 5α- (**12**) and 17% 5β-cholestan-4-one (**13**) by tlc analysis, but details were sketchy.



14, 5α
15, 5β



16, 5α
17, 5β

A possible explanation for the contradictory reports in the steroid work was that the substance previously considered[17] to be 5α-cholestan-4-one was in fact a near-equilibrium mixture of the 5α and 5β isomers. It was decided, therefore, to prepare a sample of the compound by methods that would assure stereochemical purity, and remeasure the equilibrium.

In the previous equilibration study,[17] the sample of 5α-cholestan-4-one used was prepared from cholest-4-ene by a sequence of hydroboration, oxidation of the crude product with acetic acid–chromium trioxide, and chromatography on alumina. As 5β-cholestan-4-one was reported to epimerize on basic alumina, the possibility existed that cocrystallization of the 5α and 5β epimers had occurred, even though the sample was nicely crystalline, and the melting point behavior was judged to be satisfactory at the time. Pure samples of the cholestan-4-ones were therefore prepared, and the equilibrium was restudied.

Discussion

Cholest-4-ene was prepared from cholesterol by standard methods.[34,35] Hydroboration afforded a mixture of the epimeric 4 alcohols (72%). The mixture was partially

Table II
Optical Rotation Data for Pure Compounds[a,b]

Sample	Wavelength	[α]	n	m	s.d. (est)
5α-Cholestan-4-one (A)	307.5	−809.0	5	21	3.7
	267.0	1664.2	5	21	4.3
	Amplitude	2473.2			4.0
5α-Cholestan-4-one (B)	307.5	−813.8	1	8	0.4
	267.0	1668.7	1	8	1.4
	Amplitude	2482.5			1.0
Mean values	307.5	−811.4			2.6
	267.0	1666.5			3.2
	Amplitude	2478.4			2.9
5β-Cholestan-4-one	307.5	+352.6	3	11	6.6
	267.0	+256.5	3	11	8.5
	Amplitude	−96.1			

[a] n = number of separately weighed samples; m = number of ORD measurements; s.d. (est) = upper estimates of the variance in the mean rotations arising from the variance of the individual measurements. [b] See ref 42.

separated by column chromatography on alumina and fractional crystallization to give the known 5α-cholestan-4α-ol (27%) and a mixture of 5α-cholestan-4α-ol and 5β-cholestan-4β-ol (73%) as previously reported by Jones,[20] *et al.* Oxidation of 5α-cholestan-4α-ol under Jones conditions afforded 5α-cholestan-4-one. 5β-Cholestan-4-one was prepared both by fractional crystallization of the product of Jones oxidation of the mixed alcohols[20] and by BF_3-catalyzed rearrangement of 5α-cholestane 4α,5-epoxide.[36] The possibility that the 5α-cholestan-4-one might undergo epimerization under Jones oxidation conditions was ruled out by the observation that Jones oxidation of the mixed 5β-cholestan-4-ols from lithium aluminum hydride reduction of 5β-cholestan-4-one led to regeneration of the 5β-4 ketone. The two independent preparations of 5β-cholestan-4-one provide some assurance of the purity of the compound. The 5α- and 5β-4 ketones could be readily separated on tlc, and the samples used in the equilibration study were free from impurities by this criterion. The physical properties of the ketones are in accordance with previous reports. In particular the ORD curves reported here (Experimental Section) agree quite well with the data reported by Djerassi[37] for these compounds, deviations being generally in the sense of a greater magnitude of rotation.

An attempt to study the equilibrium by vpc was foiled by the facility of thermal isomerization[24] at the temperatures required for vpc (about 220°). However, the vpc study failed to reveal any components other than the epimeric cholestan-4-ones. Equilibrium was approached from both sides using acid and base catalysis at 25°, and the equilibrium mixtures were analyzed by ORD.[24] The mean rotations at 307.5 and 267 nm and the amplitude of the Cotton effect in each case are listed in Table II and III for the pure compounds and the equilibrium mixtures.

The equilibrium mixture of cholestan-4-ones (**12, 13**) was estimated to consist of 87.4% (84.9–91.1%) 5α- (**12**) and 12.6% (8.9–15.1%) 5β-cholestan-4-one (**13**) (in ethanol at 25°). This agrees well with the reports of Djerassi[18] and Robinson[19] and also with the previously reported[17,24,25] result for the 6 ketone. It seems clear now that the sample of 5α-cholestan-4-one used in the earlier ORD measurements[17] was in fact an equilibrium mixture.

With this experimental discrepancy resolved we can now turn to the force-field calculations. Minimum energy all-chair conformations and their corresponding energies have been calculated for the 1-decalone structures (**1–9**) and the androstan-4-one (**14, 15**) and androstan-6-one (**16, 17**) structures as models of the cholestanone systems (**10–13**). This process has also been carried out for the parent hydrocarbons for comparison purposes. The calculated energy differences are found to be in reasonable agreement with the available experimental data in all cases. (See Table I).

The question of the high percentage of the cis isomer in the equilibrium mixtures of the bicyclic 1-decalone compounds (**1–9**) compared with the steroidal analogs (**10–17**) is now largely resolved by noting that there are two different low-energy cis conformers, cis equatorial (**2**) and cis axial (**3**), accessible in each of the bicyclic *cis*-1-decalone

Table III
Optical Rotation Data For Equilibrium Mixtures

Sample, reagent	Wavelength	[α]	n	m	s.d. (est)	Est % 5β	C[a]
5α-Cholestan-4-one (A)							
Base	307.5	−658.8	2	16	5.1	13.1 ± 0.5[b]	1.04
	267.0	1453.8			6.7	15.1 ± 0.5	
	Amplitude	2112.5			8.4	14.2 ± 0.3	
Acid	307.5	−654.8	3	24	3.6	13.5 ± 0.4	1.02
	267.0	1464.3			5.7	14.3 ± 0.4	
	Amplitude	2119.1			5.9	14.0 ± 0.2	
5α-Cholestan-4-one (B)							
Base	307.5	−672.9	2	16	5.1	11.9 ± 0.5	1.01
	267.0	1489.0	2	12	7.0	12.6 ± 0.5	
	Amplitude	2162.3	2	12	8.6	12.3 ± 0.3	
Acid	307.5	−682.2	1	4	7.6	11.1 ± 0.7	0.96
	267.0	1540.5	1	4	9.4	8.9 ± 0.7	
	Amplitude	2222.7	1	4	12.1	9.9 ± 0.5	
5β-Cholestan-4-one							
Base	307.5	−662.4	3	16	5.7	12.8 ± 0.5	1.03
	267.0	1467.0			13.7	14.1 ± 1.0	
	Amplitude	2129.4			14.6	13.6 ± 0.6	
Acid	307.5	−671.4	3	20	4.5	12.0 ± 0.4	0.98
	267.0	1507.9			14.1	11.2 ± 1.0	
	Amplitude	2179.3			14.3	11.6 ± 0.6	
Mean values	307.5					12.4 ± 0.5	
	267.0					12.7 ± 0.9	
	Amplitude					12.6 ± 0.7	

[a] C = volumetric correction factor necessary if observed rotations were due to a mixture of pure 5α- and 5β-cholestan-4-one. [b] Estimated standard deviation in the estimated percentage of 5β-cholestan-4-one arising from variance in rotations.

systems (2, 3; 5, 6; 8, 9) and only one in each of the steroid cases (11, 13, 15, 17). The recent report by House[41] that the equilibrium mixture of *cis*- and *trans*-7α-*tert*-butyl-1-decalone contains only about 5% of the cis compound is in keeping with this interpretation, as only one low-energy cis conformer is accessible in this system. This statistical effect is sufficient to result in an excess of *cis*-9-methyl-1-decalone (5, 6) in the calculated equilibrium mixture at room temperature, despite the slightly lower steric energy for the trans isomer 4 (in contrast to Klyne's early prediction[7]).

Very little experimental information is available on the conformational preferences of the *cis*-1-decalone systems. Djerassi has concluded from ORD data[27] that the cis axial conformer (9) is favored in *cis*-10-methyl-1-decalone, and the cis equatorial conformer is favored in both *cis*-1-decalone (2) and *cis*-9-methyl-1-decalone (5). Guy and Wintermitz[28] have adduced nmr data to support the latter conclusion. The calculations predict the cis equatorial conformer to be favored in each case (2, 5, 8), but for the angular methyl compounds the energy difference is slight, and substantial amounts of each conformer are predicted at room temperature.

Zalkow,[43] *et al.*, have shown that ketal formation in steroid 3 ketones can be quantitative in anhydrous acidic alcohol solutions. Ketal formation was found to be less extensive in ethanol than in methanol, to be significantly decreased by an equatorial alkyl substituent adjacent to the ketone, and to be very sensitive to added water. In 95% ethanol–water the extent of ketal formation under acid-catalyzed equilibration conditions should be less than 0.5%. Precautions were taken against condensation and oxidation side reactions under basic equilibration conditions.

The rotations listed in Tables II and III are the mean values for several sets of measurements as indicated, and the standard deviations quoted are (upper) estimates of the standard deviation in the mean arising from the variance in and between the individual measurements. Some of the values differ by large amounts compared to the estimated standard deviations, so that systematic errors cannot be completely ruled out. However, varying the time for equilibration showed no effects attributable to side reactions, and the two samples of 5α-cholestan-4-one which gave slightly different equilibration results gave ORD curves which were identical within experimental limits.

Estimated equilibrium compositions are listed in Table III in terms of the percentage of 5β-cholestan-4-one, for the different samples and reaction conditions. Analysis of the errors showed that to a first approximation proportional errors were large compared to constant errors in the rotations. Thus the determination at 307.5 nm is inherently more accurate, as the rotation change is the greatest at this wavelength.

Conclusions

The present work removes the previous inconsistencies concerning the stabilities of 1-decalone ring systems, and is in agreement with our earlier conclusion, that force-field calculations can give results with accuracy competitive with experiment for molecules and properties such as discussed here, and any serious difference between calculation and experiment does not necessarily reflect on the accuracy of the calculation, but may well be the fault of the experiment.

Experimental Section

Melting points were determined with a Fisher-Johnson hot-stage apparatus. Optical rotatory dispersions were measured with a Cary 60 recording spectropolarimeter.

Cholestan-4-ols.[20,44] To a stirred solution of 5 g (13.5 mmol) of cholest-4-one[35] (prepared from cholest-4-en-3-one[34]) in 50 ml of tetrahydrofuran at 0° was added a solution of diborane (about 25 mmol) in 25 ml of tetrahydrofuran. The reaction mixture was stirred at room temperature for 1 hr. Excess reagent was quenched by the addition of 2 ml of water; then 3 ml of 3 *N* aqueous NaOH was added, followed by 20 ml (233 mmol) of 30% hydrogen peroxide. The mixture was stirred at room temperature for 2 hr and extracted with ether. The ether extract was washed with water, acidified aqueous potassium iodide solution, aqueous sodium thiosulfate solution, dilute aqueous sodium bicarbonate solution, water, and saturated aqueous NaCl, and dried (Na_2SO_4). The solvent was evaporated under reduced pressure. Column chromatography of the residue on neutral alumina (activity IV) followed by fractional crystallization from methanol–ether yielded 1.0 g (21.3%) of 5α-cholestan-4α-ol, mp 188–189°, $[\alpha]^{26}$D +4.4 + 0.2° (*c* 0.959, $CHCl_3$) (lit.[44] mp 187–188°, $[\alpha]$D +3°). The remaining material (2.7 g) was a mixture of 5α-cholestan-4α-ol and another component, presumably[20] 5β-cholestan-4β-ol (51.4%) by tlc and vpc.

5α-Cholestan-4-one. To a stirred solution of 1.02 g (2.6 mmol) of 5α-cholestan-4α-ol in 50 ml of acetone (Baker Analyzed) at room temperature, 8 *M* chromic acid was added dropwise until a permanent red color appeared. The mixture was stirred for 10 min, and the reaction was quenched with saturated aqueous sodium metabisulfate solution. The mixture was added to 200 ml of water and extracted twice with ether. The ether extracts were washed with water, dilute aqueous sodium bicarbonate solution, again with water, and saturated aqueous NaCl, and dried (Na_2SO_4). The solvent was evaporated under reduced pressure and the residue was combined and crystallized from methanol–ether to yield 0.60 g (59%) of 5α-cholestan-4-one: mp 98–100° (lit.[45] mp 99–99.5°); ORD (95% C_2H_5OH) $[\alpha]_{267}$ +1664° (max), $[\alpha]_{307.5}$ 809° (min) [lit.[46] ORD $[\alpha]_{267.5}$ +1650° (max), $[\alpha]_{307.5}$ −780° (min)].

5β-Cholestan-4-one. To a stirred solution of 1.2 g (3.1 mmol) of mixed cholestan-4-ols (predominantly 5β-cholestan-4β-ol by tlc and vpc) in 50 ml of acetone (Baker Analyzed) at room temperature, 8 *M* chromic acid was added dropwise until a permanent red color appeared. The mixture was stirred for 10 min, and the reaction was quenched with saturated aqueous sodium metabisulfite solution. The mixture was added to 200 ml of water and extracted twice with ether. The ether extracts were washed with water, dilute aqueous sodium bicarbonate solution, with water again, and with saturated NaCl solution, and dried (Na_2SO_4). The solvent was evaporated under reduced pressure and the combined residues were crystallized from methanol–ether, yielding 0.65 g (54%) of 5β-cholestan-4-one: mp 110–111° (lit.[37] mp 111–112°); ORD (95% C_2H_5OH) $[\alpha]_{309}$ +350.9° (max), $[\alpha]_{304}$ +344.2° (min), $[\alpha]_{299}$ +360.3°, $[\alpha]_{275}$ +233.4° [lit.[37] ORD $[\alpha]_{300}$ +318° (max), $[\alpha]_{277.5}$ +240° (min)].

5β-Cholestan-4-one.[36] To a solution of 5α-cholestane 4α,5-epoxide (210 mg, 0.543 mmol) in dry benzene (30 ml) at room temperature was added BF_3–Et_2O (0.375 ml, 325 mg, 2.29 mmol, distilled off CaH_2). The reaction was quenched after 50 sec by the addition of aqueous Na_2CO_3. The crude product, isolated with ether, was crystallized repeatedly from methanol–ether to give 5β-cholestan-4-one (66 mg, 0.171 mmol, 31%) as needles, mp and mmp 108–109°.

5α-Cholestane 4α,5-Epoxide. To a solution of cholest-4-ene (0.25 g, 0.675 mmol) in dry ether (10 ml) at 0° was added a solution of monoperphthalic acid (20 mmol) in ether (10 ml). The reaction mixture was allowed to stand at 0° for 4 days and quenched with aqueous $NaHCO_3$. The ether layer was separated, washed with dilute aqueous $NaHCO_3$ and water, and dried over saturated aqueous NaCl and anhydrous $MgSO_4$. Evaporation of the solvent under reduced pressure and repeated crystallization from acetone gave 5α-cholestane 4α,5-epoxide (110 mg, 0.285 mmol, 42%), mp 98–99° (lit.[21] mp 100–101°).

A Preliminary Test of the Modified Jones Oxidation Conditions. Preparation of 5β-Cholestan-4-ol and Regeneration of 5β-Cholestan-4-one. One gram of 5β-cholestan-4-one (mp 108°) in ether was added dropwise to a slurry of ether and 1 g of $LiAlH_4$. The reaction mixture was stirred at room temperature overnight. The excess $LiAlH_4$ was destroyed by water under a nitrogen atmosphere. Saturated ammonium chloride solution was then added, the reaction mixture was filtered, and the filtrate was extracted with ether and dried over anhydrous sodium sulfate. After removal of the ether, the white solid residue (0.95 g) showed two spots on thin layer chromatography (R_f 19, 26 in ethyl acetate), which were interpreted as

the axial and equatorial alcohols resulting from the $LiAlH_4$ reduction. The infrared spectrum showed hydroxyl stretching but no carbonyl stretching. Since both the coprostan-4α-ol and the coprostan-4β-ol would yield the same ketone, coprostan-4-one, upon oxidation, the alcohol mixture was not separated or purified any further.

The crude alcohol mixture (1.4 g, 3.2 mmol) was dissolved in 300 ml of acetone and oxidized at 19–21° by adding 1.6 ml of 8 *N* chromic acid reagent dropwise during 45 min. The solution was allowed to stand for 3 hr, and then was poured into water. The precipitate was collected and taken up in $CHCl_3$. The chloroform layer was washed and dried, and the solvent was evaporated *in vacuo*. The product was recrystallized from acetone, yield of 1.2 g, mp and mmp with authentic sample (mp 108°) 106°.

Equilibration of the Ketones. Standard solutions of the ketones were prepared by use of a Mettler H20 T balance and calibrated graduated flasks. Solutions were kept in a thermostat at 25° throughout. The ORD curves for the pure ketones were recorded for solutions in 95% ethanol (previously distilled off NaOEt to remove traces of aldehydes), in a jacketed 1-cm quartz cell at 26.3–26.4°. Solutions of the ketones were made up in the same way, except that 0.1 *M* KOH in ethanol or about 0.1 *M* HCl in ethanol were used instead of ethanol. Equilibrations were allowed to proceed at 25° under nitrogen. Concentrations were chosen to give the greatest possible amplitude on the recording chart on the 1° scale (about 60 mg in 10 ml for 5α-cholestan-4-one; about 20–30 mg in 10 ml for the less soluble 5β-cholestan-4-one). ORD curves were measured for the equilibrating solution after 3 hr for the base-catalyzed equilibrations, and after 7 days for the acid-catalyzed equilibrations. The amplitude of the Cotton effect and the magnitude of the rotation at 267 and 307.5 nm was recorded in each case, and the percentage of 5β-cholestan-4-one in the equilibrium mixture was calculated in the usual manner.[24]

References and Notes

(1) Paper XCVIII: C. J. Finder, M. G. Newton and N. L. Allinger, *Acta Crystallogr.*, in press.
(2) This work was supported in part by Grant No. AM-14042 from the National Institutes of Health, and was taken in part from the Ph.D. dissertation of G. L. Wang, Wayne State University, 1968. Inquiries should be directed to the University of Georgia.
(3) R. B. Turner, *J. Amer. Chem. Soc.*, **74**, 2118 (1952).
(4) W. G. Dauben, O. Rohr, A. Labbauf, and F. D. Rossini, *J. Phys. Chem.*, **64**, 283 (1960).
(5) N. L. Allinger and J. L. Coke, *J. Org. Chem.*, **26**, 2096 (1961).
(6) E. J. Corey and R. A. Sneen, *J. Amer. Chem. Soc.*, **77**, 2505 (1955).
(7) W. Klyne, *Experientia*, **12**, 119 (1956).
(8) N. L. Allinger and J. H. Siefert, *J. Amer. Chem. Soc.*, **94**, 8082 (1972).
(9) W. Hueckel, *Justus Liebigs Ann. Chem.*, **441**, 1 (1925).
(10) A. Ross, P. A. S. Smith, and A. Dreiding, *J. Org. Chem.*, **20**, 905 (1955).
(11) H. E. Zimmerman and A. Mais, *J. Amer. Chem. Soc.*, **81**, 3644 (1959).
(12) C. H. Heathcock, R. Ratcliffe, and J. Van, *J. Org. Chem.*, **37**, 1796 (1972).
(13) M. Hanack, C. E. Harding, and J.-L. Derocque, *Chem. Ber.*, **105**, 421 (1972).
(14) F. Sondheimer and D. Rosenthal, *J. Amer. Chem. Soc.*, **80**, 3995 (1958).
(15) B. Rao and L. Weiler, *Tetrahedron Lett.*, 927 (1971).
(16) J. A. Marshall and A. R. Hochstetler, *J. Amer. Chem. Soc.*, **91**, 648 (1969).
(17) N. L. Allinger, M. A. DaRooge, and R. B. Hermann, *J. Org. Chem.*, **26**, 3626 (1961).
(18) J. Gutzwiller and C. Djerassi, *Helv. Chim. Acta*, **49**, 2108 (1966).
(19) C. H. Robinson and L. Milewich, *J. Org. Chem.*, **36**, 1812 (1971).
(20) J. R. Bull, E. R. H. Jones, and G. D. Meakins, *J. Chem. Soc.*, 2601 (1965).
(21) C. W. Shoppee, M. E. H. Howden, R. W. Killick, and G. H. R. Summers, *J. Chem. Soc.*, 630 (1959).
(22) (a) R. Stevenson and L. F. Fieser, *J. Amer. Chem. Soc.*, **78**, 1409 (1956); (b) H. B. Henbest and T. I. Wrigley, *J. Chem. Soc.*, 4596 (1957).
(23) (a) J. R. Bull, *J. Chem. Soc. C*, 1128 (1969); (b) D. N. Jones, J. R. Lewis, C. W. Shoppee, and G. H. R. Summers, *J. Chem. Soc.*, 2876 (1955); (c) J. E. Bridgeman, P. C. Cherry, W. R. T. Cottrell, E. R. H. Jones, P. W. LeQuesne, and G. D. Meakins, *Chem. Commun.*, 561 (1966).
(24) (a) D. N. Jones and D. E. Kime, *J. Chem. Soc. C*, 846 (1966); (b) D. N. Jones, R. Grayshan, and D. E. Kime, *ibid.*, 48 (1969); (c) D. N. Jones, R. Grayshan, A. Hinchcliffe, and D. E. Kime, *ibid.*, 1208 (1969); (d) D. J. Jones, K. J. Wyse, and D. E. Kime, *ibid.*, 2763 (1971).
(25) D. N. Jones and R. Grayshan, *J. Chem. Soc. C*, 2421 (1970).
(26) H. Velgova, V. Cerny, and F. Sorm, *Collect Czech. Chem. Commun.*, **37**, 1015 (1972), and references cited therein.
(27) (a) C. Djerassi and D. Marshall, *J. Amer. Chem. Soc.*, **80**, 3986 (1958); (b) W. Klyne, Colloqium at Montpelier, *Bull. Soc. Chim. Fr.*, 1396 (1960); (c) W. Moffit, R. B. Woodward, A. Moscowitz, W. Klyne, and C. Djerassi, *J. Amer. Chem. Soc.*, **83**, 4013 (1961); (d) C. Djerassi and J. Staunton, *ibid.*, **83**, 736 (1961).
(28) E. Guy and F. Winternitz, *Ann. Chim. (Paris)*, **57** (1969).
(29) (a) M. Hanack, "Conformation Theory," Academic Press, New York, N. Y., 1965; (b) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Wiley-Interscience, New York, N. Y., 1965.
(30) N. L. Allinger, M. T. Tribble, M. A. Miller, and D. H. Wertz, *J. Amer. Chem. Soc.*, **93**, 1637 (1971).
(31) N. L. Allinger, M. A. Miller, J. Hirsch, and I. Tyminski, *J. Amer. Chem. Soc.*, **91**, 337 (1969).
(32) (a) N. L. Allinger, M. T. Tribble, and M. A. Miller, *Tetrahedron*, **28**, 1173 (1972); (b) N. L. Allinger and M. T. Tribble, *ibid.*, **28**, 1191 (1972).
(33) W. D. Cotterill and M. J. T. Robinson, *Tetrahedron*, **20**, 905 (1964).
(34) J. F. Eastham and R. Teranishi, "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 192.
(35) J. Broome, B. R. Brown, A. Roberts, and A. M. S. White, *J. Chem. Soc.*, 1406 (1960).
(36) B. N. Blackett, J. M. Coxon, M. P. Hartshorn, and K. E. Richards, *Tetrahedron*, **25**, 4999 (1969).
(37) C. Djerassi, R. Riniker, and B. Riniker, *J. Amer. Chem. Soc.*, **78**, 6362 (1956).
(38) N. L. Allinger and J. L. Coke, *J. Amer. Chem. Soc.*, **81**, 4080 (1959).
(39) C. G. Frye and A. W. Weithamp, *J. Chem. Educ.*, **14**, 372 (1969).
(40) N. L. Allinger and F. Wu, *Tetrahedron*, **27**, 5093 (1971).
(41) H. O. House and M. J. Umen, *J. Org. Chem.*, **27**, 2841 (1972).
(42) The ORD machine was equilibrated at 26.3–26.4°. This temperature difference would give a change of about 0.1% in the mole fraction of 5α-cholestan-4-one at equilibrium, which is small compared to other variations in the data.
(43) L. H. Zalkow, R. Hale, K. French, and P. Crabbé, *Tetrahedron*, **26**, 4947 (1970).
(44) S. Wolfe, M. Nussim, Y. Mazur, and F. Sondheimer, *J. Org. Chem.*, **24**, 1034 (1959).
(45) L. Ruzicka, P. A. Plattner, and M. Furrer, *Helv. Chim. Acta.*, **27**, 727 (1944).
(46) C. Djerassi, W. Closson and A. E. Lippman, *J. Amer. Chem. Soc.*, **78**, 3163 (1956).

Chemistry of Some Tricyclic Cyclopropyl Halides

David B. Ledlie,* Jeffry Knetzer, and Amy Gitterman[1]

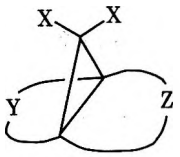
Department of Chemistry, Middlebury College, Middlebury, Vermont 05753

Received September 25, 1973

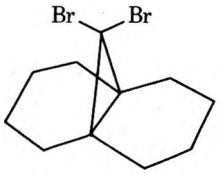
The silver ion assisted methanolysis of 2, 3, and 4 has been studied. Both rates and products are reported. Comments are made as to the effect of neighboring sites of unsaturation on relative reactivities. The effect of complexed silver ion on reactivity is also discussed.

The chemistry of cyclopropyl systems of the general type 1 has been the subject of several recent studies.[2-7] Herein we report on the chemistry of systems of this type, namely, the silver ion assisted solvolysis of **2**, **3**, and **4**. Our immediate goal was to ascertain the reaction pathways available to systems in which the normal disrotatory

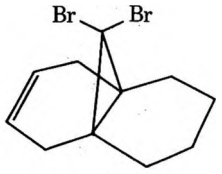
mode of ring opening is apparently prohibited under solvolytic conditions. We were also interested in the role played by neighboring sites of unsaturation, as well as the effect of complexed silver ion on the rate of solvolysis of **3** and **4**.



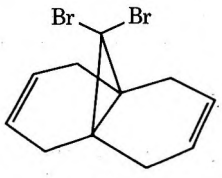
1



2



3

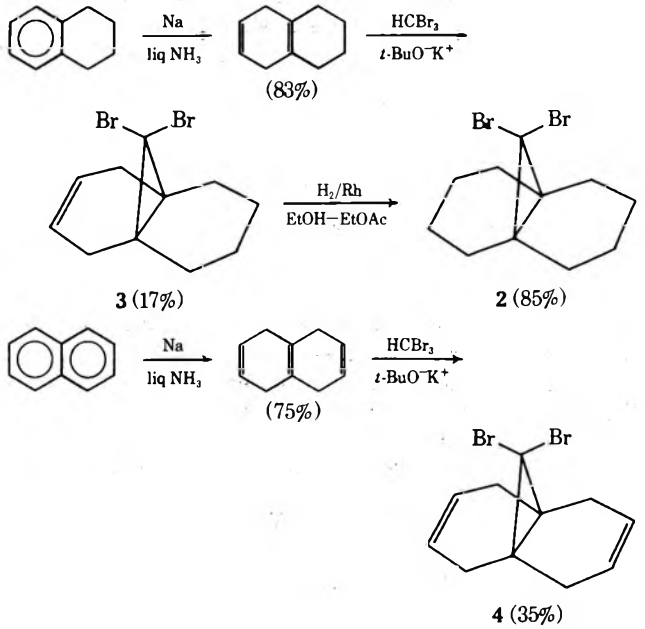


4

Results

Synthesis of the compounds required for this investigation is outlined in Scheme I. Although the overall yield of **2** is only 12%, our method of synthesis is much less arduous than previously published procedures.[8,9]

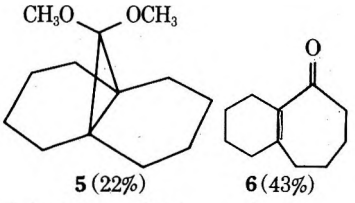
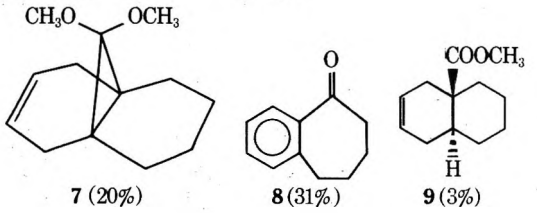
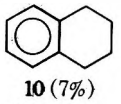
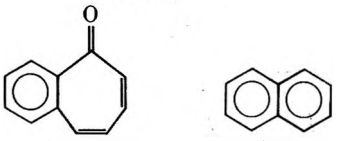
Scheme I



Product studies were carried out by reacting the compound in question with an excess of silver ion ($AgNO_3$) in methanol until all starting material had been consumed. An internal standard was added and the reaction mixture was analyzed *via* gas chromatography. The results obtained are contained in Table I.

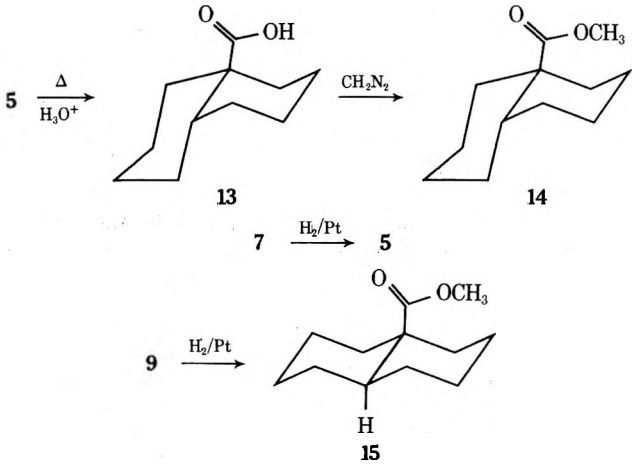
Compounds **8**, **10**, **11**, and **12** were identified by comparison of their ir spectra with those of authentic materials.[11] The structure of **6** was assigned on the basis of spectral data and a correct elemental analysis.[6] Structures **5**, **7**, and **9** were assigned on the basis of the various chemical conversions outlined in Scheme II as well as spectral evidence.[12a] The infrared spectra of both **14** and **15** are identical with those of authentic materials.[12b]

Table I
Products Obtained in the Silver Ion Assisted Solvolysis of 2, 3, and 4

Compd	Products
2	 5 (22%) 6 (43%) + others (~10%)[a]
3	 7 (20%) 8 (31%) 9 (3%)
	 10 (7%)
4	 11 (2–5%) 12 (2–5%)

[a] While these products were not rigorously identified, it is believed that they consist of a mixture of **14** and **15**. This is based solely on infrared evidence.

Scheme II



Rate studies were carried out in 95% methanol using approximately a 20-fold excess of silver ion ($AgClO_4$). The standard ampoule technique was employed to determine pseudo-first-order rate constants (k_1) which were then converted to second-order rate constants (k_2) by dividing k_1 by the initial silver ion concentration. The results are contained in Table II.

Discussion

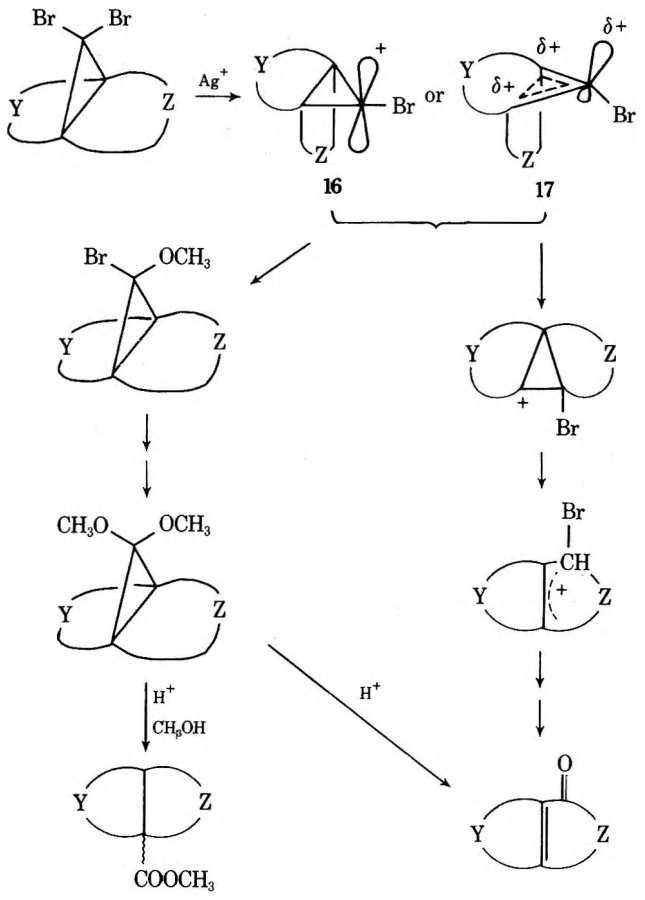
The majority of products obtained in this investigation can be rationalized as arising from a cyclopropyl cation (**16**) or a partially opened species (**17**)[13] (see Scheme III).

Table II
Rate Constants and Activation Parameters of the Silver Ion Assisted Solvolysis of 2, 3, and 4

Compd	Temp, °C[b]	k, l. mol^{-1} min^{-1}	ΔH^*, kcal mol^{-1}	ΔS^*, eu	$k^{25°}$ (rel)
4	90.8	5.03×10^{-3} ($\pm$0.01)	30.3	5.7	1
	100.6	1.54×10^{-2} ($\pm$0.01)			
	25.0	4.18×10^{-7} [a]			
3	28.3	4.09×10^{-2} ($\pm$0.18)	18.0	−13.2	7×10^{4}
	42.7	1.69×10^{-1} ($\pm$0.05)			
	25.0	2.90×10^{-2} [a]			
2	11.00	3.68×10^{-1} ($\pm$0.09)	12.9	−23.3	3×10^{6}
	22.6	9.33×10^{-1} ($\pm$0.12)			
	25.0	1.12[a]			

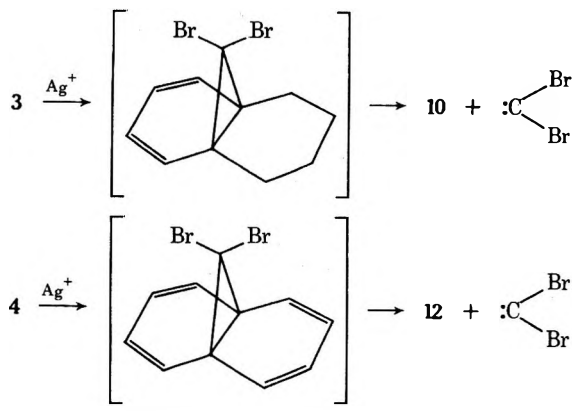
[a] This is an extrapolated value. [b] At least two runs were made at each temperature.

Scheme III

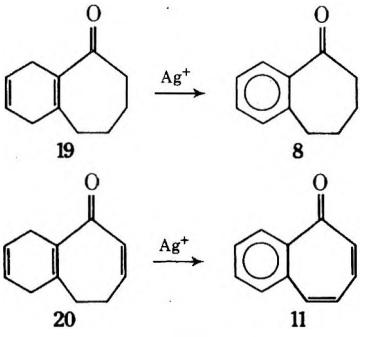


The origin of the aromatic compounds **10** and **12** finds precedence in the experiments reported by Vogel.[14] A possible mode of formation is outlined in Scheme IV.

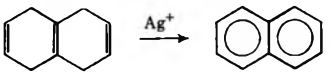
Scheme IV



It is surmised that **8** and **11** arise from a silver ion oxidation of **19** and **20**, respectively.

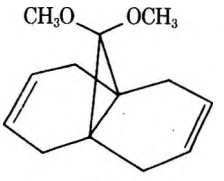


Calculations indicate that in the gas phase these reactions are thermodynamically feasible.[15,16] In addition we have also demonstrated that silver ion and a trace of nitric acid in either methanol or diglyme quantitatively converts triene **21** to naphthalene (eq 1).



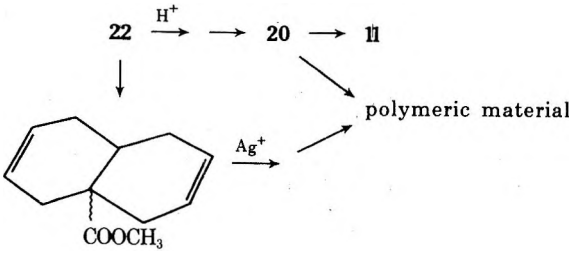
(1)

It is puzzling, at first glance, as to why such low yields of volatile products are obtained when **4** is solvolyzed. One must also offer an explanation for the absence of ketal **22**



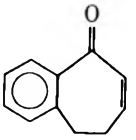
as a reaction product. While **2** and **3** are quite reactive at room temperature, **4** requires a temperature of ~100° for an extended period of time in order to react completely. We suggest that under these conditions (acid is produced as the reaction proceeds) **22** is unstable. Several reaction pathways available to **22** are illustrated in Scheme V.

Scheme V



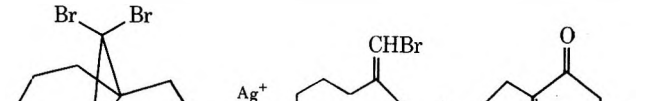
Buchanan has demonstrated that the ketone **23** is unstable at room temperature and rapidly polymerizes.[17] Thus if **23** is an intermediate in the formation of **11**, and **22** is unstable to the reaction conditions, one can readily

explain the low yields of volatile material, as well as the absence of ketal **22**.

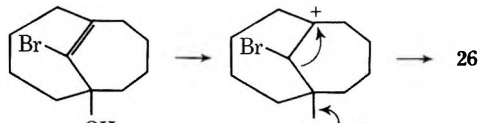


23

Recently, Reese reported on the silver ion assisted solvolysis of 10,10-dibromotricyclo[4.3.1.$0^{1,6}$]decane (**25**)[4] (see eq 2). The major product, **26**, can be explained as resulting from fragmentation of the protonated intermediate **29**.[18] No products of this type were obtained in the solvolysis of **2**, **3**, or **4**. This can be readily rationalized if one peruses the heats of reaction for the conversions contained in Table III.[19] As pointed out by Warner, the feasibility or net exothermicity of the conversion of a tricyclic cyclopropyl system to a bicyclic bridgehead olefin *via* a disrotatory ring opening depends on the magnitude of the strain energy inherent in the olefinic system in question as well as the exothermicity of the conversion listed in Table III.[3] For example, Warner calculates a strain energy of approximately 20 kcal in **31**. However, the exothermicity calculated in eq 4 is 29 kcal. Thus a net exothermicity of 9–10 kcal is calculated for the conversion of **30** to **31**.



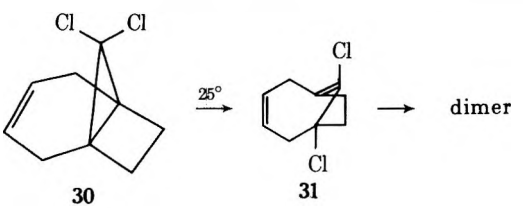
25 **26** (50%) **27** (15%) (2)



28 **29** **26**

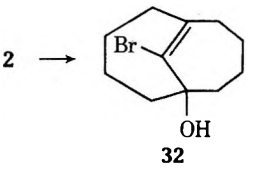
Table III
Calculated Heats of Reaction for the Conversion of Several Bicyclic Systems to the Corresponding Monocyclic Olefin

Reaction	ΔH, kcal mol^{-1}
(eq 3)	−14.50
(eq 4)	−29.10
	−10.10
	−2.20



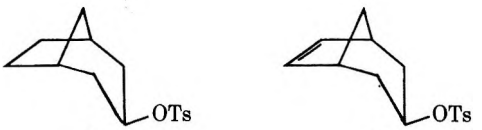
30 **31** dimer

Using a similar treatment one calculates the conversion of **25** to **28** to be endothermic by 9–10 kcal and the conversion of **2** to **32** to require an activation energy of approximately 20 kcal/mol^{-1}.[20a] Compounds **2**, **3**, and **4** therefore do not undergo reactions similar to **25** since lower energy reaction pathways are available.



2 → **32**

It now remains to explain the differences in relative rates observed in the solvolysis of **2**, **3**, and **4**. Le Bel has reported on the solvolytic behavior of the bicyclic tosylates **33** and **34**.[20b] It was found that **33** was three times more reactive than **34** at 25°. This corresponds to a difference in ΔG^* of 0.65 kcal/mol^{-1}. This difference can be ascribed solely to an inductive effect. The disposition of the double bond in **34** in relation to the leaving groups is similar to that found in **3**. However, the difference in ΔG^* between **2** and **3** is 2.10 kcal/mol^{-1}. The difference between these values [(2.10–0.65) = 1.45 kcal/mol^{-1}] is then a measure either of distabilization of the transition state in the ionization of **3** due to complexing of silver ion with the site of unsaturation[21] or relief of steric strain in the transition state in the ionization of **2** or some combination of these two factors. If the effect is completely inductive, then one would predict a difference in ΔG^* between **3** and **4** of 4.2 kcal/mol^{-1} (*e.g.*, 2 × 2.1 kcal/mol^{-1}). This differs from the observed value by 2.4 kcal, a factor of ~60 in rate.[24]



33 **34**

If, on the other hand, the difference in rate was due to relief of steric strain plus the normal inductive effect of two uncomplexed double bonds, one calculates a difference in ΔG^* between **3** and **4** of 2.75 kcal/mol^{-1} [1.45 + (2)(0.65)] which differs from the observed value by 3.9 kcal/mol^{-1}, a factor of ~750 in rate. The former explanation thus seems more palatable. Perhaps the deviation between the observed and calculated rates for **4** (a factor of 20–60) is a result of the conformation of the system which allows for a more stable silver–olefin complex and more efficient electron withdrawal by silver ion.

It should also be noted that rate and product studies indicate no participation by double bond in either **3** or **4**.

Experimental Section[25]

1,2,3,4,5,8-Hexahydronaphthalene. The procedure of Hückel and Worffel was employed with the exception that the reaction was carried out at −33°.[26] A yield of 67 g (83%) of material was obtained. An nmr spectrum of the product exhibited absorption at 5.45 (singlet, 2 protons), 2.40 (singlet, 4 protons), and 1.22–2.05 ppm (multiplet, 8 protons).

11,11-Dibromotricyclo[4.4.1.$0^{1,6}$]undec-3-ene (3). Compound **3** was synthesized according to previously published procedures.[10] It was obtained in a 17% yield. Its properties were identical with those reported.[10]

1,4,5,8-Tetrahydronaphthalene. The material was prepared in a 75% yield according to the method of Hückel and Schlee, mp 53–55° (lit. mp 53°).[27] An nmr spectrum of the compound exhibited absorption at 5.54 (singlet, 4 protons) and 2.44 ppm (singlet, 8 protons).

11,11-Dibromotricyclo[4.4.1.$0^{1,6}$]undecane (2). Compound **3** was reduced catalytically at atmospheric pressure [hydrogen, 5% rhodium on alumina, ethyl acetate–ethanol (1:1)] to afford **2** in an 85% yield. Its properties were identical with those previously reported.[6]

Silver Ion Assisted Methanolysis of 3. Compound **3** (1 g, 3.26 mmol) and silver nitrate (2 g, 12.5 mmol) were dissolved in 100

ml of methanol and refluxed for 2 hr. The reaction mixture was filtered to remove silver bromide, and water (150 ml) was added to the filtrate. The aqueous layer was extracted with 3 × 25 ml portions of pentane. The pentane extracts were combined and dried, and solvent was removed to afford 0.85 g of a yellow oil which was subjected to vpc analysis on a 2 ft × 0.25 in. 5% Carbowax 20M column. Four major components (**7**–**10**) were shown to be present. They were all collected. Both compounds **10** and **8** were identified by comparison of their infrared and nmr spectra with spectra of authentic materials. An nmr spectrum of compound **7** exhibited absorption at 0.90–2.56 (complex absorption, 12 protons), 3.17 and 3.24 (two singlets, 6 protons), and 5.34 ppm (broad singlet, two protons). Compound **9** exhibited infrared absorption at 3010, 1720, and 1615 cm^{-1}. In runs in which yields were determined an internal standard (biphenyl) was added directly to the reaction mixture after all starting material had been consumed. The reaction mixture was subjected to vpc analysis without further work-up (see text for a tabulation of yields).

Catalytic Hydrogenation of 9. Compound **9** was reduced at atmospheric pressure (hydrogen, PtO_2, ethanol). The usual work-up afforded a crude product which was subjected to vpc analysis. One major component (>90%) was in evidence. The material was collected and its infrared spectrum was measured; it was identical with that of compound **15**.

Catalytic Hydrogenation of 7. Compound **7** was reduced (hydrogen, PtO_2, ethanol) to afford material which had an infrared spectrum identical with that of **5**.

Silver Ion Assisted Methanolysis of 4. Compound **4** (5 g, 16.4 mmol), silver nitrate (11.2 g, 65.6 mmol), and 100 ml of methanol were placed in a high pressure apparatus and heated at 100° for 20 hr. The reaction was worked up in the usual manner to afford 1.2 g of crude material that was subjected to gas chromatographic analysis on the Carbowax column mentioned previously. Two volatile components were present and both were collected. The first to elute was identified as naphthalene (**12**) and the second was identified as benzotropone (**11**). In both cases the structures in question were assigned by comparison of infrared spectra with spectra of authentic materials. Yields were determined in the same manner as reported for the solvolysis of **3**.

Silver ion Assisted Methanolysis of 2. For complete experimental details see ref 6.

Kinetic Procedures. The standard ampoule technique was employed in all kinetic runs. All ampoules were wrapped in aluminum foil. Solvents were rigorously purified and used immediately after preparation. The concentration of silver ion (~20-fold excess in each case) was determined *via* titrametric methods. In all runs except the solvolysis of **2** at least six points were taken (four points in the case of **2** at 22.6°). Reactions were followed by determining (vpc) the amount of starting material remaining at a given time. Biphenyl was employed as the internal standard. All reactions were followed to 90% completion. Pseudo-first-order rate constants were determined using a least-squares computer program.

Acknowledgment. We wish to express our appreciation to Dr. Kirk Roberts for valuable suggestions concerning the kinetic techniques employed and to Scott Helmers for developing the computer programs which we used. Acknowledgment is also made to the Petroleum Fund, administered by the American Chemical the Research Corporation; and the National Foundation for support of this research.

Registry No.—**2**, 20564-71-0; **3**, 38760-88-2; **4**, 4578-96-5; **7**, 34201-85-9; **9**, 49744-92-5; 1,2,3,4,5,8-hexahydronaphthalene, 36231-13-7; 1,4,5,8-tetrahydronaphthalene, 493-04-9.

References and Notes

(1) NSF URP Program Fellow, summer, 1973.
(2) B. M. Trost and R. C. Atkins, *Chem. Commun.*, 1254 (1971).
(3) P. Warner, *et al.*, *J. Amer. Chem. Soc.*, **94**, 7607 (1972).
(4) C. B. Reese and M. R. D. Stebles, *Chem. Commun.*, 1231 (1972).
(5) C. B. Reese and M. R. D. Stebles, *Tetrahedron Lett.*, 4427 (1972).
(6) D. B. Ledlie, *J. Org. Chem.*, **37**, 1439 (1972).
(7) D. B. Ledlie and J. Knetzer, *Tetrahedron Lett.*, 5021 (1973).
(8) R. Vaidyanathaswamy and D. Devaprabhakana, *Chem. Ind. (London)*, **16**, 515 (1968).
(9) Our method is essentially the same as that reported by Vogel and coworkers.[10]
(10) E. Vogel, *et al.*, *Justus Liebigs Ann. Chem.*, **759**, 1 (1972).
(11) We thank Professor G. L. Buchanan for supplying us with the infrared spectrum of **11**.
(12) (a) Although this does not constitute rigorous proof of the location of the double bond in either **7** or **9**, it does establish the structure of the carbon skeleton. Mechanistic considerations lead us to believe that our assignments as to the location of unsaturation in **7** and **9** are correct. (b) These spectra were graciously supplied to us by Professor F. D. Greene.
(13) For leading reference concerning this point see ref 6.
(14) E. Vogel, *Proc. Robert A. Welch Found. Conf. Chem. Res.*, **12**, 215 (1968).
(15) S. W. Benson, *et al.*, *Chem. Rev.*, **69**, 279 (1969).
(16) P. v. R. Schleyer, J. E. Williams, and K. R. Blanchard, *J. Amer. Chem. Soc.*, **92**, 2377 (1970).
(17) G. I. Buchanan and D. R. Lockhart, *J. Chem. Soc.*, 3587 (1959).
(18) Professor Philip Warner has recently informed us of experiments in which he has trapped **28**, the precursor to **29**.
(19) Calculated from values obtained in ref 15 and 16.
(20) (a) This value is somewhat exaggerated since the strain energy in **31** would be expected to be a little larger than in **28** or **32**; (b) N. A. Le Bel and R. Maxwell, *J. Amer. Chem. Soc.*, **91**, 2307 (1969).
(21) It is well known that silver ion will complex with double bonds.[22] Dewar has depicted the bonding in the silver–olefin complex as a twofold interaction.[23] It consists of (a) an interaction between a bonding π molecular orbital of the olefin and a vacant silver s orbital and (b) an interaction between the antibonding molecular orbital of the olefin and a filled silver d orbital of the appropriate symmetry.
(22) F. R. Hartley, *Chem. Rev.*, **73**, 163 (1973), and references contained therein.
(23) M. J. S. Dewar, *Bull. Chim. Soc. Fr.*, **18**, C79 (1951).
(24) If one corrects for the amount of silver ion consumed in both ionization and oxidation processes when calculating the rates for **3** and **4**, this factor reduces to ~20.
(25) Infrared spectra were determined with a Perkin-Elmer 457 recording spectrophotometer. The nmr spectra were measured at 60 Hz with an Hitachi Perkin-Elmer R20 spectrometer using tetramethylsilane as the internal reference. All spectra were measured in CCl_4 unless otherwise stated. A Hewlett-Packard 5750B gas chromatograph was used for all vpc analysis. All peak areas were integrated with a planimeter. Magnesium sulfate was employed as the drying agent. All reactions involving air- or moisture-sensitive compounds were carried out under a nitrogen atmosphere.
(26) W. Hückel and U. Worffel, *Ber.*, **89**, 2098 (1956).
(27) W. Hückel and M. Schlee, *Chem. Ber.*, **88**, 346 (1955).

Notes

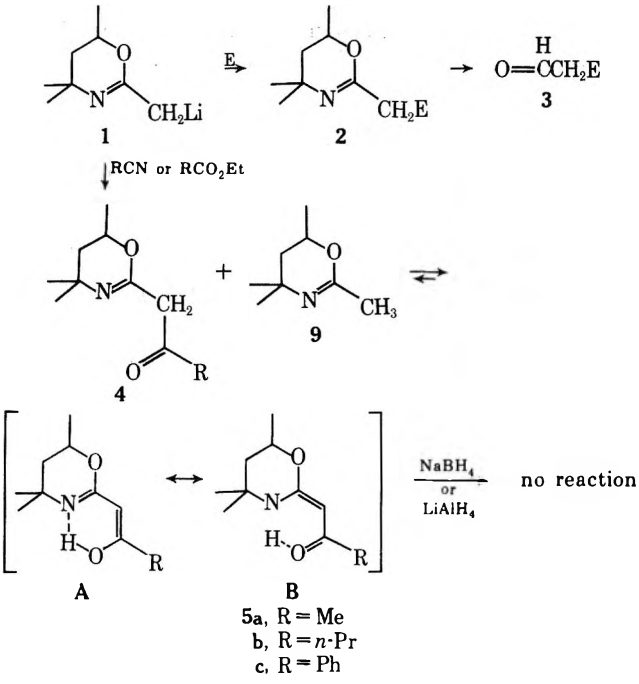
Reaction of Lithiated Oxazines with Esters and Nitriles

G. Ray Malone and A. I. Meyers*[1]

Department of Chemistry, Wayne State University, Detroit, Michigan 48202

Received August 31, 1973

Among the various electrophiles, E (alkyl halides, carbonyl compounds, and epoxides), that react with the lithiooxazine **1**[2] producing the elaborated oxazine **2**, only those derived from esters and nitriles cannot be transformed into the homologated acetaldehydes **3**. Although esters and nitriles acylated the lithio salt **1**, the resulting β-keto oxazine **4** was inert to reduction by sodium borohydride and, therefore, could not be hydrolyzed (as its tetrahydro-1,3-oxazine) to β-keto aldehydes. The reason for this limitation in the oxazine–aldehyde synthesis is due mainly to the tautomeric behavior in **4** which was found to exist mainly as the delocalized species **5**. The structures of **5a–c** were deduced from their spectral properties (Table I).



1 2 3 4 9

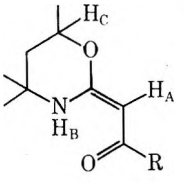
A B

5a, R = Me
b, R = *n*-Pr
c, R = Ph

Examination of the ultraviolet spectrum of the adducts **5** reveals long wavelength absorption (290–323 nm) with intense extinction coefficients (25,000–30,000) indicative of an extended conjugated chromophore. The infrared spectra for these derivatives were devoid of the typical C=N and C=O absorption bands at 1665 and 1710 cm^{-1}, respectively, while exhibiting delocalized absorption in the 1500–1610 cm^{-1} region. Further evidence that **5** and not **4** was the prevailing structure was gathered by the nmr spectrum which showed a one-proton vinyl signal as well as an NH proton that readily exchanged with deuterium oxide. This behavior is consistent with tautomerism observed in a variety of heterocyclic systems containing exocyclic β-carbonyl moieties.[3]

Recovery of the 2-methyl oxazine **9** was also noted in most cases when **1** was treated with the esters or nitriles. However, the amount of methyl oxazine recovered was always greater when acylation was performed with esters (% **9**, Table I). For esters and nitriles possessing α protons, the appearance of **9** could be due to simple proton abstraction by **1** as a competitive reaction mode to addition. When benzonitrile or ethyl benzoate was used as the acylating agent, no α protons were present and yet 29% of **9** was still formed. Since the pK_a of the methyl group in acetonitrile and ethyl acetate have been estimated to be comparable (~25),[4] the greater recovery of **9** from ester

Table I
Reaction of 1 with Nitriles and Esters to Give 5 and 9

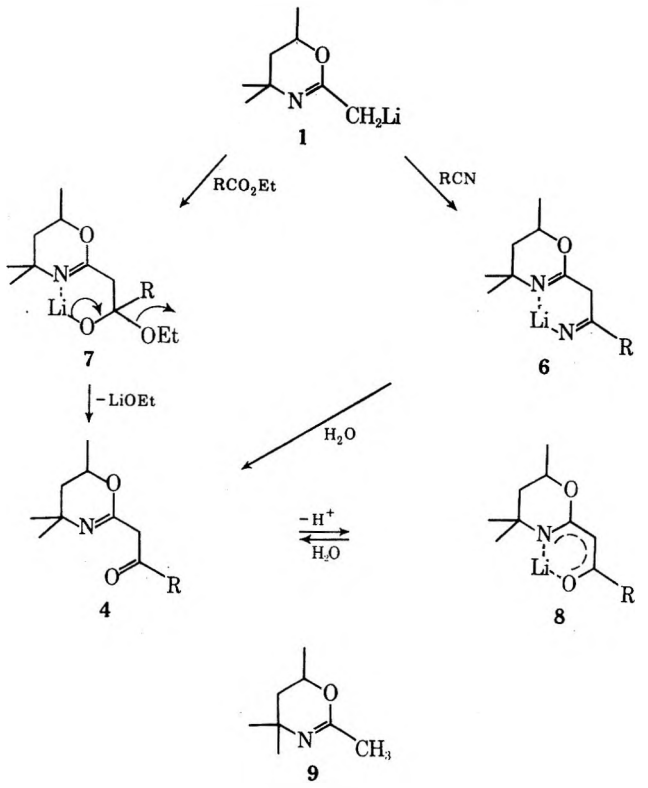


5

Nitrile[a] or ester		% 5[b]	Mp,[c,d] °C	% 9[b]	Uv (EtOH), nm (ε)	5 Ir (KBr), cm^{-1}	5 Nmr (CCl_4) H_A	H_B	H_C
MeCN	**5a**	70	64.5	30	293 (2.5 × 10⁴)	1510 1550	4.5 (s, 1)	11.6 (b, 1)	4.3 (m, 1)
$MeCO_2Et$		50		50		1610			
n-PrCN	**5b**	85	53	15	291 (2.4 × 10⁴)	1500 1548	4.5 (s, 1)	11.8 (b, 1)	4.3 (m, 1)
n-$PrCO_2Et$		60		40		1610			
PhCN	**5c**	100	85		323 (3.1 × 10⁴) 231 (1.6 × 10⁴)	1510 1540	5.2 (s, 1)	12.3 (b, 1)	4.3 (m, 1)
$PhCO_2Et$		71		29		1580 1600			

[a] Reactions run on a 0.02-mol scale. [b] Vpc ratios; isolated yields slightly lower. [c] Recrystallized from petroleum ether. [d] Elemental analysis: Calcd for $C_{10}H_{17}NO_2$ (**5a**): C, 65.54; H, 9.35; N, 7.64. Found: C, 65.28; H, 9.52; N, 7.60. Calcd for $C_{12}H_{21}NO_2$ (**5b**): C, 68.21; H, 10.02; N, 6.63. Found: C, 67.97; N, 9.94; N, 6.57. Calcd for $C_{15}H_{19}NO_2$ (**5c**): C, 73.44; H, 7.81; N, 5.71. Found: C, 73.63; H, 7.73; N, 5.74.

acylation must be due to proton abstraction from 4 generating the lithio salt 8. Hence, 4 must be formed directly in the reaction medium. When acylation was performed using the nitrile, the initial intermediate is probably 6 which is much less acidic than 4 and the latter is not produced until the reaction is quenched. It is, therefore, concluded that acylations of oxazine carbanions are more efficiently performed using nitriles as the acylating agent.



Experimental Section[5]

α-Ketoalkyloxazines 5. General Acylation Procedure. A solution of **9** (0.02 mol) in 30 ml of tetrahydrofuran was cooled to −78° in Dry Ice–acetone and treated with 0.021 mol (1.6 *M*) of *n*-butyllithium (hexane). The system was under a nitrogen atmosphere throughout the addition. The anion **1** appeared within 1 hr as a yellow suspension and the ester or nitrile (0.21 mole) was added all at once. The reaction was allowed, while stirring, to warm to room temperature (8–15 hr) and then poured into water and acidified (1 *N* hydrochloric acid). The aqueous acid solution was extracted with ether–pentane (1:1) and the extracts were discarded. The aqueous solution was neutralized with 5% sodium bicarbonate and extracted with ether, dried (Na_2SO_4), and concentrated. The residue was recrystallized from petroleum ether to afford pure **5** (see Table I for physical constants).

Acknowledgment. The authors are grateful to the National Science Foundation (GP 22541), the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the National Institutes of Health for financial support of this work. Generous supplies of organolithium reagents from the Lithium Corporation of America are also gratefully acknowledged.

Registry No. —**1**, 50311-32-5; **5aA**, 50311-33-6; **5aB**, 50311-34-7; **5bA**, 50311-35-8; **5bB**, 50311-36-9; **5cA**, 50311-37-0; **5cB**, 50311-38-1; **9**, 26939-18-4; MeCN, 75-05-8; $MeCO_2Et$, 141-78-6; *n*-PrCN, 109-74-0; *n*-$PrCO_2Et$, 105-54-4; PhCN, 100-47-0; $PhCO_2Et$, 93-89-0.

References and Notes

(1) Address all correspondence to this author at the Department of Chemistry, Colorado State University, Fort Collins, Colorado 80521.
(2) A. I. Meyers, A. Nabeya, H. W. Adickes, I. R. Politzer, G. R. Malone, A. C. Kovelesky, R. L. Nolen, and R. C. Portnoy, *J. Org. Chem.*, **38**, 36 (1973).
(3) R. Mondelli and L. Merlini, *Tetrahedron*, **22**, 3253 (1966).
(4) H. O. House, "Modern Synthetic Reactions," 2nd ed, W. A. Benjamin, New York, N. Y., 1972, p 494.
(5) Melting points and boiling points are uncorrected. Analyses were performed by Midwest Microlabs, Indianapolis, Ind. Infrared, ultraviolet, and nmr spectra were recorded on Perkin-Elmer 257 and 202 and Varian T-60 instruments, respectively. Vapor phase chromatography was performed on a Hewlett-Packard 5750 using UCW-98 (80–100 mesh) columns.

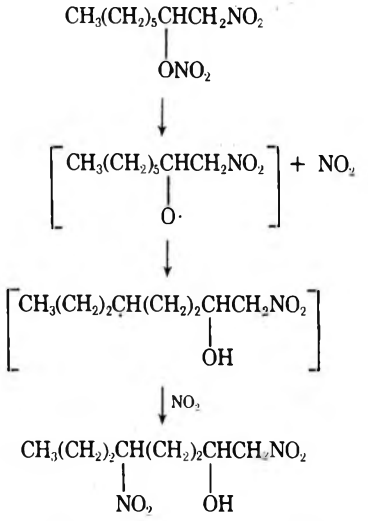
Thermal Decomposition of β-Nitroalkyl Nitrates in Olefinic Solvents

J. M. Larkin, W. M. Cummings,* and K. L. Kreuz

Texaco Research Center, Beacon, New York 12508

Received September 7, 1973

Kreuz and Larkin have shown that β-nitroalkyl nitrates decompose in paraffinic and aromatic solvents by a homolytic fission of the $O-NO_2$ bond, intramolecular rearrangement, and recombination to give dinitro alcohols.[1] Facile reaction requires somewhat higher temperatures for secondary (140–160°) than for tertiary (100–130°) nitrate structures.



Subsequent studies in our laboratories have demonstrated that a different decomposition path may be followed when olefinic solvents are employed. Thus, when 1-nitro-2-octyl nitrate was heated in dodecene-1 at 138°, a more rapid decomposition occurred than in dodecane ($T_{1/2}$ 20 min *vs.* 2300 min). In addition, infrared analysis showed that a conjugated nitro olefin was forming instead of a 1,5-dinitro alcohol.

Product isolation was facilitated when the nitro nitrate, *e.g.*, 1-nitro-2-decyl nitrate, was heated in octene-1 at 123° for an extended period (8 hr). After removal of the solvent under reduced pressure, followed by chromatography of the residue on silica gel with hexane as eluent, 1-nitro-1-decene was isolated in 90% yield. Also isolated was a mixture of nitrogen-containing materials and evidently (from nmr analysis) solvent derived. In order to determine the importance of solvent nitration as a source of nitro olefin, 1-nitro-2-octyl nitrate was decomposed in 2,4,4-trimethylpentene-1. No nitro olefin derived from the solvent could be detected by nmr analysis of the product [lack of broadening of one of the doublet lines centered at δ 7.86 and absence of a methyl absorption near δ 8.22 $[-C(CH_3)=CHNO_2]$.

Table I gives the products formed and their yield as determined by isolation or nmr analysis for the decomposition of various β-nitroalkyl nitrates. One sees that secon-

Table I
Products Formed in the Decomposition of β-Nitroalkyl Nitrates in Octene-1 at 120°

β-Nitroalkyl nitrate	Registry no.	Nitro olefin	Registry no.	Yield,[a] %
1-Nitro-2-pentyl nitrate	49746-21-6	1-Nitro-1-pentene	3156-72-7	90 (nmr)
1-Nitro-2-hexyl nitrate	14202-68-7	1-Nitro-1-hexene	49746-23-8	90 (nmr)
1-Nitro-2-octyl nitrate	13434-64-5	1-Nitro-1-octene	4550-05-4	90 (nmr)
1-Nitro-2-decyl nitrate	36601-57-7	1-Nitro-1-decene	36601-60-2	90 (isolated)[b]
1-Nitro-2-methyl-2-pentyl nitrate	35223-51-9	1-Nitro-2-methyl-1-pentene	49746-25-0	50 (nmr)[c]
1-Nitro-2,4,4-trimethyl-2-pentyl nitrate	32778-22-6	1-Nitro-2,4,4-trimethyl-1-pentene	27838-96-6	15[d]
2-Octyl nitrate	7214-64-4	No reaction		

[a] Yield was determined by comparing the nmr absorptions at δ 7.86 and 9.15 ($CH{=}CHNO_2$) to the absorptions at δ 4.68 (CH_2NO_2), or the absorptions at δ 7.85 [$C(CH_3){=}CHNO_2$] to the absorption at δ 4.82 (CH_2NO_2) in the crude product after the olefin was removed under vacuum. [b] 1-Nitro-1-decene typified 1-nitro 1-olefins in exhibiting two intense absorptions in the ir at 6.55 and 7.3 μ. The structure displayed below gives the proton assignments as determined by nuclear magnetic resonance.

$$\underset{0.90}{CH_3}(\underset{1.30}{CH_2})_6\underset{2.26}{CH_2}\underset{8.15}{CH}{=}\underset{7.86}{CHNO_2}$$

Saturation of the absorbing nuclei at δ 2.26 causes the absorption at δ 8.15 to become a doublet. [c] Other major product formed was 2-methyl-1,5-dinitro-2-pentanol in 50% yield (nmr). [d] Isolated in the combined chromatographic fractions containing the nitro olefin and 2,4,4-trimethyl-1,5-dinitro-2-pentanol. The overall yield is probably lower than 15% since some dinitro alcohol remains on the column.

Table II
Kinetic Data for the Thermal Decomposition of 1-Nitro-2-Decyl Nitrate[a]

1-Nitro-2-decyl nitrate	Solvent	Temp, °C	$k_\psi \times 10^5$, sec^{-1} [b]
0.11	Dodecene-1	116	1.7
0.11	Dodecene-1	121	4.1
0.11	Dodecene-1	140	58
0.16	Dodecene-1	121	4.3
0.23	Dodecene-1	121	4.6
0.11	50% dodecene-1 50% dodecane	121	2.1

[a] Data obtained after induction period. [b] Pseudo-first-order rate constant. The decomposition was followed by monitoring the disappearance of the 11.6-μ band in the infrared. The reproducibility of the rate constant was ±5%.

Table III
Variation of Pseudo-First-Order Rate Constants for the Decomposition of 0.11 *M* 1-Nitro-2-Decyl Nitrate at 123°

Olefin solvent	$k_\psi \times 10^5$, sec^{-1}
Hexachloropropylene	0.38[a]
Dodecene-1	5.1
n-Decyl vinyl ether	23

[a] The rate of decomposition was so slow that an induction period was not detectable.

dary nitrates go cleanly to nitro olefins but that tertiary nitrate structures tend more to the rearrangement path which leads to dinitro alcohols. In fact, decomposition of 1-nitro-2,4,4-trimethyl-2-pentyl nitrate gives no more than 15% nitro olefin along with 85% of the radical rearrangement products, mostly 1,5-dinitro-2,4,4-trimethyl-2-pentanol. 1-Nitro-2-methyl-2-pentyl nitrate gives equal amounts of the nitro olefin along with 1,5-dinitro-2-methyl-2-pentanol. The importance of the nitro group is shown by the failure of 2-octyl nitrate to react under these conditions.

When a secondary β-nitroalkyl nitrate is heated, there is an induction period prior to decomposition.[2] This induction period is temperature dependent (being ~2 hr at 120° and ~10 min at 140°). There is no detectable change in the induction period when nitrobenzene is added to the reaction mixture, or when the reaction solution is deaerated with nitrogen. The induction period remains when *n*-decyl vinyl ether is used as a solvent in place of the hydrocarbon olefin. The cause of this inhibition is not known: no compositional changes were noted during the period by infrared monitoring. Since β-nitroalkyl nitrates are not amenable to the more conventional methods of purification[3] such as distillation and crystallization, there may be a small amount of impurity which is acting as an inhibitor and must be consumed before reaction can occur.

(For the tertiary systems, there is no apparent induction period, since the rearrangement reaction is also operative and is consuming nitrate.)

During the first half-life after the induction period, approximate first-order kinetics seem to be obeyed, as the half-life does not change appreciably with change in initial concentration of β-nitroalkyl nitrate. However, by halving the concentration of dodecene-1 (by diluting with an equal volume of dodecane, an inert solvent) the apparent rate constant is halved, indicating a dependency of the reaction on olefin concentration. See Table II. The rate of decomposition after the induction period is also affected by changes in the structure of the olefin solvent. This variation is given in Table III.

There seems to be a parallelism between the basicity of the olefin and the size of the rate constant, the largest value being associated with the strongest electron-donating solvent, *n*-decyl vinyl ether, and the smallest with the electron-poor solvent, hexachloropropylene. Decomposition of 1-nitro-2-decyl nitrate did not occur when heated with diphenyl ether under similar conditions. This indicates that the ether linkage *per se* is not sufficient to induce decomposition.

For the secondary systems (assuming that the induction period in the olefin-induced decomposition is due simply to some impurity causing inhibition) the overall data suggest that a bimolecular reaction is occurring which involves the solvent. The need for an activated hydrogen and apparent dependency upon the basicity of the olefin all lead to the thought that this elimination is proceeding by some type of acid–base sequence.

Experimental Section

The infrared spectra were obtained with a Perkin-Elmer 137B double-beam recording spectrophotometer using thin films on sodium chloride disks, or differentially in solution in 0.1-mm sodium chloride cells. Nuclear magnetic reasonance spectra were de-

termined with a Varian Associates H-100 spectrometer at 100 HMz with tetramethylsilane as the internal standard.

β-Nitroalkyl Nitrates. The compounds used in this study were prepared by the nitric oxide reduction of β-nitroalkyl peroxynitrates formed by the action of nitrogen dioxide and oxygen on the appropriate olefin according to the method of Lackowicz and Kreuz.[4]

1-Nitro 1-Olefins. A typical example for the preparation of 1-nitro 1-olefins is given below.[5] To 100 ml of octene was added 5.0 g of 1-nitro-2-decyl nitrate and this solution was heated at reflux for 12 hr. The solvent was removed under reduced pressure to give 4.7 g of a complex mixture. This mixture was transferred to a column containing 200 g of silica gel. Elution of the column with hexane gave in the initial fractions 3.4 g of 1-nitro-1-decene (90%). Subsequent elution with methanol gave 0.8 g of a solvent-derived nitrogen-containing mixture of compounds.

Kinetics. The appropriate amount of β-nitroalkyl nitrate was added to the olefin solution and the unstirred solutions were heated to the desired temperature. The decompositions of the β-nitroalkyl nitrates were followed by monitoring the disappearance of the 6.1-, 7.8-, and 11.6-μ infrared absorption bands. The solutions of β-nitroalkyl nitrates followed Beer's law in the concentration ranges studied (up to 0.22 *M*). The temperatures were maintained at ±0.5°. Aliquots were withdrawn at timed intervals and their spectra were recorded differentially in 0.1-mm sodium chloride cells *vs.* the appropriate solvent. A base-line, straddling the peak, technique was used to measure the absorbances of the band being monitored.[6] The rate constants were calculated from the slope of a log (β-nitroalkyl nitrate)/β-nitroalkyl nitrate *vs.* time plot and were reproducible within ±5%.

Inspection of all crude reaction mixtures was done by comparison of their infrared and nuclear magnetic resonance spectra with spectra of authentic samples of 1-nitro 1-olefins. The preparation and properties of the authentic 1-nitro 1-olefins is described by Cummings and Kreuz.[2]

Registry No.—2-Methyl-1,5-dinitro-2-pentanol, 49746-26-1.

References and Notes

(1) J. M. Larkin and K. L. Kreuz, *J. Org. Chem.*, **37**, 3079 (1972).
(2) W. M. Cummings and K. L. Kreuz, *J. Org. Chem.*, **37**, 3929 (1972).
(3) They are purified by column chromatography on silica gel and the purity is established by chemical analysis, nmr, and ir. Therefore, small amounts of impurity could easily go undetected.
(4) D. R. Lachowicz and K. L. Kreuz, *J. Org. Chem.*, **32**, 3885 (1967); U. S. Patent 3,282,983 (1966).
(5) U. S. Patent 3,510,531 (1900).
(6) H. Morgan, R. M. Sherwood, and T. A. Washall, *Anal. Chem.*, **38**, 1009 (1966).

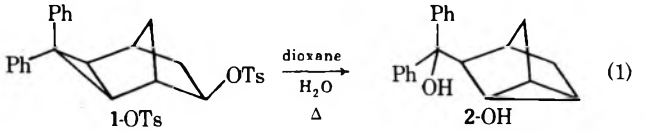
On the Solvolysis Pathway for *exo*-3,3-Diaryltricyclo[3.2.1.0^{2,4}]oct-*exo*-6-yl Tosylates[1,2]

James W. Wilt* and John R. Flanyak

Department of Chemistry, Loyola University of Chicago, Chicago, Illinois 60626

Received October 1, 1973

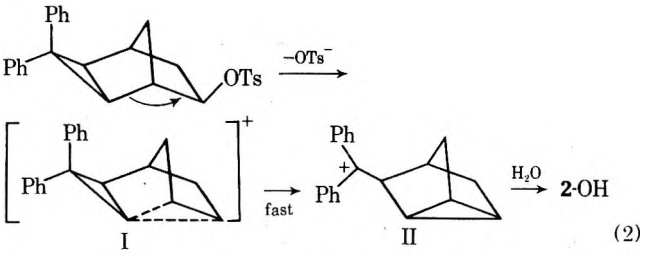
The solvolytic rearrangement of the parent title tosylate 1-OTs leads to a nortricyclyl product 2-OH (eq 1).[3] Two



1-OTs 2-OH (1)

8-OH (Ph = *p*-chlorophenyl

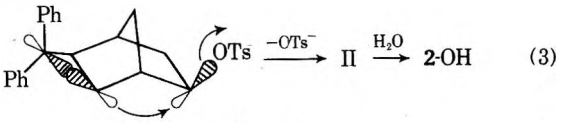
pathways were suggested[3] for this process. The first suggestion (pathway A) invoked a 1,2 σ-bond participation in the rate-determining step to produce ion I as an intermediate species (eq 2). It was further suggested that in a subsequent fast step, I was converted to the more stable benzhydrylic cation II, which then gave the alcohol product 2-OH. Such σ participation should be absent in the endo tosylate related to 1-OTs. Indeed, the exo/endo



(2)

pathway A

rate ratio for the epimeric tosylates was over 4000-fold at 25°.[3] A second suggested pathway (pathway B) invoked direct cyclopropyl ring participation *via* a "back-lobe" mechanism to produce ion II at once (eq 3). This idea would also accommodate a large exo/endo rate ratio. Moreover, such a notion has literature precedent,[4] as pathway A obviously has as well.

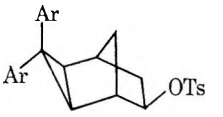


(3)

pathway B

It has now been found that pathway A seems to be in better accord with further results. Use of aryl groups in 1-OTs other than phenyl allowed a structure-reactivity study. Table I contains some of the results of that study.[5]

Table I
Kinetic Data on Tricyclic Tosylates, 64.5° [a]

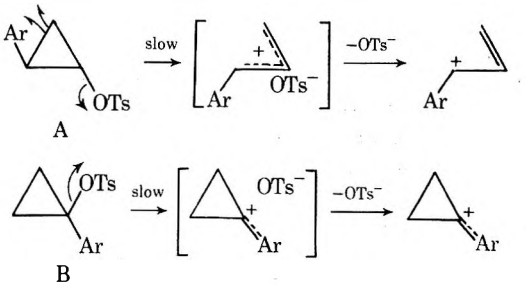


Compd	Ar	$10^5 k_1$, sec^{-1}	k_{rel}
3-OTs	*p*-Anisyl	28.85	27
4-OTs	*p*-Tolyl	15.97	15
5-OTs	*p*-Chlorophenyl	1.07	1

[a] In dioxane–water (80:20, v/v) containing 2,6-lutidine.

A plot of log k_1 *vs.* 2σ[6] gave a value of $\rho = -1.44 \pm 0.04$. Use of σ^+[7] values gave a poor correlation with pronounced curvature. Clearly, the rate correlation with σ instead of σ^+ and the small spread in k_{rel} are in better keeping with pathway A, wherein no appreciable cationic charge development on the aromatic ring; so the reaction wherein direct conjugation with the aryl groups exists in ion II.

A comparison might be made with the arylcyclopropyl systems shown in eq 4.[8] In A, solvolysis occurs with little

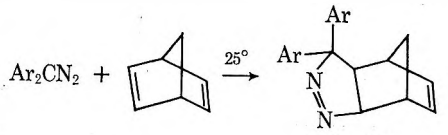


(4)

charge development on the aromatic ring, so the reaction follows σ and $\rho = -1.75$ (108°). In B, solvolysis occurs with extensive charge development on the aromatic ring; so the reaction follows σ^+ and $\rho = -4.31$ (108°). It is suggested that pathway A of the present study relates to A and pathway B relates to B.

As another point for investigation, one might note that a fundamental difference between the pathways lies in the

Table II
Diaryldiazomethane–Norbornadiene Adducts

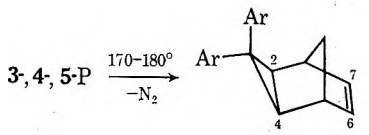


3-, 4-, 5-P

Ar	Mp, °C	Yield, %	Calcd, % C	Calcd, % H	Found, % C	Found, % H
p-Anisyl, **3**-P[a]		40				
p-Tolyl, **4**-P	121–122.5	44	84.05	7.05	84.08	7.19
p-Chlorophenyl, **5**-P	131–132	39.5	67.62	4.53	67.64	4.42

[a] Used crude in the subsequent steps.

Table III
***exo*-3,3-Diaryltricyclo[3.2.1.$0^{2,4}$]-oct-6-enes**

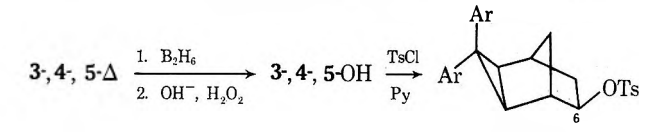


3-, 4-, 5-Δ

Ar	Mp, °C	Yield, %	Calcd, % C	Calcd, % H	Found, % C	Found, % H
p-Anisyl, **3**-Δ[a]	76–77.5	88	82.99	6.96	83.19	6.90
p-Tolyl, **4**-Δ[b]	110–112	92	92.25	7.74	92.07	7.96
p-Chlorophenyl, **5**-Δ[c]	134.5–136	97	73.41	4.92	73.35	4.84

[a] δ H-2,4, 1.63 (s); δ H-6,7, 6.53 (t). [b] δ H-2,4, 1.71 (s); δ H-6,7, 6.50 (t). [c] δ H-2,4, 1.53 (s); δ H-6,7, 6.51 (t).

Table IV
***exo*-3,3-Diaryltricyclo[3.2.1.$0^{2,4}$]-oct-*exo*-6-yl Tosylates**

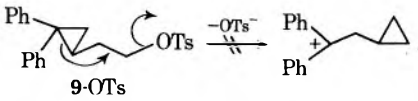


3-, 4-, 5-OTs

Ar	Mp, °C	Yield, %	Calcd, % C	Calcd, % H	Found, % C	Found, % H
p-Anisyl, **3**-OTs[a]	84–87 dec	74	71.00	6.16	70.93	6.37
p-Tolyl, **4**-OTs[b]	100.5–103 dec	84	75.95	6.58	76.20	6.62
p-Chlorophenyl, **5**-OTs[c]	116–118 dec	86	64.93	4.84	65.15	4.74

[a] δ H-6, 4.51 (br d). [b] δ H-6, 4.51 (br d). [c] δ H-6, 4.52 (br d). Note: the alcohols **3**- and **5**-OH were used in crude form to prepare these tosylates. Alcohol **4**-OH had mp 129–131° from hexane. *Anal.* Calcd for $C_{22}H_{24}O$: C, 86.80; H, 7.94. Found: C, 87.06; H, 8.06.

participation suggested: a norbornyl type in A but a cyclopropyl ring type in B. If pathway B operated in eq 1, then perhaps β-(*gem*-diphenylcyclopropyl)ethyl tosylate (**9**-OTs) would behave similarly, as in eq 5. This tosylate



9-OTs (5)

was prepared in a straightforward fashion which requires no discussion (see Experimental Section). In 80% dioxane, however, it was found that **9**-OTs solvolyzed without rearrangement; *i.e.*, only 9-OH was obtained ($k_1 = 2.5 \times 10^{-6}$ sec^{-1} at 75°), presumably *via* S_N solvolysis.[9,12] Likewise, acetolysis of **9**-OTs proceeded without rearrangement to the acetate 9-OAc. While these negative results do not disprove the existence of pathway B in eq 1, the failure of **9**-OTs to rearrange *coupled with* the low ρ value found for eq 1 make this pathway definitely less likely. On the other hand, these same facts are accommodated by pathway A, which is therefore suggested as the operative route in eq 1.

Experimental Section

Melting points, spectra, and analyses were obtained as previously described.[3] Boiling points are uncorrected. See Tables II–IV for selected characterization data. For complete nmr and ir spectral data, consult the dissertation of J. R. F.

Tosylates **3**-, **4**-, and **5**-OTs were prepared from the corresponding alcohols in pyridine with *p*-toluenesulfonyl chloride. The alcohols **3**-, **4**-, and **5**-OH, their alkene precursors **3**-, **4**-, and **5**-Δ, and the pyrazoline adducts **3**-, **4**-, and **5**-P, obtained from norbornadiene and the appropriate diaryldiazomethane that served as starting points for these syntheses, were all prepared as described for the diphenyl analog.[3] Analytical samples of the pyrazolines and alkenes were recrystallized from methanol. The tosylates were recrystallized from petroleum ether (bp 30–60°)–benzene mixtures.

β-(*gem*-Diphenylcyclopropyl)acetonitrile. Into a stirred solution of sodium cyanide (0.13 g, 2.6 mmol) in dimethyl sulfoxide (10 ml) at 60° was added dropwise a solution of (*gem*-diphenylcyclopropyl)carbinyl tosylate [mp 67–68° (lit.[14] mp 58–80°), 1.0 g, 2.6 mmol] in dimethyl sulfoxide (5 ml). The reaction material was held at 60° for 32 hr and then poured into water and extracted with ether. Distillation of the dried ether extracts gave the nitrile as an oil (0.58 g, 92%): bp 148–152° (0.35 mm); $n^{28}D$ 1.5772; d_4^{26} 1.112; ir (neat) λ 4.54 μ (CN).

Anal. Calcd for $C_{17}H_{15}N$: C, 87.51; H, 6.48. Found: C, 87.61; H, 6.63.

Methyl β-(*gem*-Diphenylcyclopropyl)acetate. The nitrile above (2.0 g, 8.5 mmol) in alcohol (15 ml) was added in portions over 15 min to a solution of potassium hydroxide (7.0 g, 0.125 mol) in water (10 ml). After an overnight reflux period, the solution was cooled and acidified. The crude acid so precipitated (1.75 g, 88%) was used directly in the next step. The acid (1.51 g, 6 mmol) in ether was esterified with excess diazomethane. Distillation afforded the ester as an oil (1.20 g, 76%): bp 151–155° (0.4 mm); $n^{28}D$ 1.5602; d_4^{26} 1.242; nmr ($CDCl_3$) δ 3.62 (s, OCH_3); ir (neat) λ 5.84 μ (C=O).

Anal. Calcd for $C_{18}H_{18}O_2$: C, 81.17; H, 6.81. Found: C, 81.11: H, 6.83.

β-(*gem*-Diphenylcyclopropyl)ethyl Alcohol (9-OH). The acetate ester above (1.2 g, 4.5 mmol) in ether (25 ml) was added dropwise over a 15-min period to lithium aluminum hydride (0.17 g, 4.5 mmol) in ether (25 ml). The solution was stirred under reflux for 3 hr and processed in the usual way. Distillation yielded the alcohol as an oil (1.05 g, 77%): bp 153–158° (0.25 mm); $n^{28}D$ 1.5913; d_4^{26} 1.210; nmr ($CDCl_3$) δ 3.68 (t, $-CH_2OH$); ir (neat) λ 3.02, 9.43–9.69 μ (primary alcohol).

Anal. Calcd for $C_{17}H_{18}O$: C, 85.68; H, 7.61. Found: C, 85.62; H, 7.50.

β-(*gem*-Diphenylcyclopropyl)ethyl Tosylate (9-OTs). Reaction of the alcohol above in pyridine with *p*-toluenesulfonyl chloride in the standard manner[15] gave tosylate **9-OTs** as a colorless solid; mp 95–97° from absolute alcohol; nmr ($CDCl_3$) δ 4.10 (t, $-CH_2OTs$); ir (KBr) λ 8.38, 8.47 μ ($-SO_2-$).

Anal. Calcd for $C_{24}H_{24}O_3S$: C, 73.44; H, 6.16. Found: C, 73.29; H, 6.27.

Solvolysis Studies. A. In Dioxane–Water (80:20 v/v). The kinetic and preparative solvolyses were performed as described earlier.[3] From 4-OTs at 110° for 24 hr there was obtained **bis(*p,p'*-dimethyl)benzhydrylidenenortricyclene (6, 99%)**: mp 103–105° from aqueous methanol; nmr ($CDCl_3$) δ 7.07 (narrow m, ArH), 2.56 (broad s, H-4), 2.33 (s, $ArCH_3$), 1.85–1.26 (m, remaining H's); ir (KBr, prominent absorptions only) λ 6.12, 6.68, 7.32, 7.90, 8.62, 9.25, 9.80, 10.01, 10.69, 11.45, 12.62, 13.10–13.41, 14.25 μ. The spectra were closely analogous to those reported[3] for benzhydrylidenenortricyclene (7).

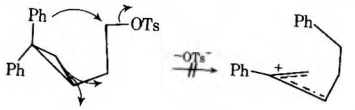
From 5-OTs at 75° for 14 hr there was obtained 8-OH (88%): mp 98–100° from aqueous methanol; nmr ($CDCl_3$) δ 7.65–7.03 (m, ArH), 2.55 (broad s, OH), 2.38 (broad s, H-4), 2.07 (d, exo H-5, $J_{exo\text{-}endo}$ = 11 Hz), 1.47 (broad s, H-1), 1.38–0.82 (m, remaining H's); ir (KBr, prominent absorptions only) λ 2.85, 6.81, 7.24, 7.70, 7.81, 8.12, 8.76, 9.35, 10.20, 10.41, 11.25, 12.43–12.72, 14.10–14.55 μ. The spectra were in close analogy to those reported for 2-OH.[3] From tosylate 9-OTs at 130° for 16 hr there was obtained only 9-OH (77%).

B. In Acetic Acid. Tosylate 9-OTs (0.19 g, 0.8 mmol) was heated in dry acetic acid (20 ml) containing sodium acetate (0.04 *M*) at 120° for 46 hr. Reaction work-up yielded only 9-OAc (0.17 g, 87%): nmr ($CDCl_3$) δ 4.05 (t, $-CH_2OAc$, J = 7.5 Hz), 1.91 (s, -OAc); ir neat) λ 5.90 μ (C=O). The nmr total spectrum was in close correspondence to 9-OH and 9-OTs and left no doubt that all three possessed the same parent structure.

Registry No.—3-OTs, 50323-69-8; 3-P, 50323-89-2; 3-OH, 50323-71-2; 3-Δ, 50323-72-3; 4-OTs, 50323-73-4; 4-P, 50323-90-5; 4-OH, 50323-74-5; 4-Δ, 50323-75-6; 5-OTs, 50323-76-7; 5-P, 50323-91-6; 5-OH, 50323-77-8; 5-Δ, 50323-78-9; 6, 50323-92-7; 8-OH, 50323-93-8; 9-OH, 38674-45-2; 9-OTs, 50323-95-0; 9-OAc, 50323-96-1; di-*p*-anisyldiazomethane, 1221-72-3; di-*p*-tolyldiazomethane, 1143-91-5; di-*p*-chlorophenyldiazomethane, 1143-92-6; norbornadiene, 121-46-0; β-(*gem*-diphenylcyclopropyl)acetonitrile, 50323-99-4; β-(*gem*-diphenylcyclopropyl)carbinyl tosylate, 50324-00-0; methyl β-(*gem*-diphenylcyclopropyl)acetate, 38674-44-1.

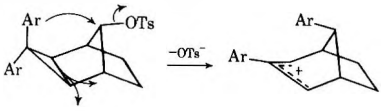
References and Notes

(1) (a) Studies on 3,3-Diaryltricyclo[3.2.1.$2^{,4}$]octanes. III. (b) Paper II: J. W. Wilt, T. P. Malloy, P. K. Mookerjee, and D. Sullivan, *J. Org. Chem.*, in press.
(2) Taken from portions of the dissertation of J. R. F., 1973.
(3) J. W. Wilt and T. P. Malloy, *J. Org. Chem.*, **38**, 277 (1973).
(4) P. K. Freeman, D. M. Balls, and J. N. Blazevich, *J. Amer. Chem. Soc.*, **92**, 2051 (1970).
(5) The extensive kinetic data for other temperatures and the activation parameters calculated therefrom have been omitted from Table I for the sake of brevity. The interested reader should inquire or consult the dissertation of J. R. F.
(6) The presence of two identical aryl groups in such studies has normally been handled in this fashion. *Cf.* H. H. Jaffé, *Chem. Rev.*, **53**, 191 (1953).
(7) H. C. Brown and Y. Okamoto, *J. Amer. Chem. Soc.*, **80**, 4979 (1958).
(8) P. v. R. Schleyer, W. F. Sliwinski, G. W. Van Dine, U. Schollkopf, J. Paust, and K. Fellenberger, *J. Amer. Chem. Soc.*, **94**, 133 (1972).
(9) β-(Cyclopropyl)ethyl brosylate itself gave no rearrangement during acetolysis.[10] The same is true for 9-OTs, either in aqueous dioxane or in dry acetic acid. Formolysis of 9-OTs was not investigated, but rearrangement would not be unexpected here. Various substituted β-(cyclopropyl)ethyl brosylates (as well as the parent) do rearrange during solvolysis in this medium.[10,11]
(10) R. R. Sauers and R. W. Ubersax, *J. Org. Chem.*, **31**, 495 (1966).
(11) M. J. S. Dewar and J. M. Harris, *J. Amer. Chem. Soc.*, **92**, 6557 (1970).
(12) It might be noted that this solvolysis of 9-OTs involved no proximate aryl migration coupled with cyclopropyl ring opening, as in eq i.



(i)

Such behavior characterizes the solvolysis of the more rigid exo-3,3-diaryltricyclo[3.2.1.$0^{2,4}$]oct-*anti*-8-yl tosylates (eq ii).[1b,13]



(ii)

(13) J. W. Wilt and T. P. Malloy, *J. Amer. Chem. Soc.*, **92**, 4747 (1970).
(14) H. M. Walborsky, L. Barasch, A. E. Young, and F. J. Impastato, *J. Amer. Chem. Soc.*, **83**, 2517 (1961).
(15) R. S. Tipson, *J. Org. Chem.*, **9**, 235 (1944).

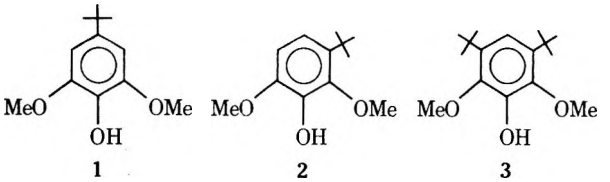
Novel Products from Oxidation of Hindered Phenols with One-Electron-Transfer Oxidants

R. C. Eckert,[1a] Hou-min Chang,*[1b] and W. P. Tucker[1c]

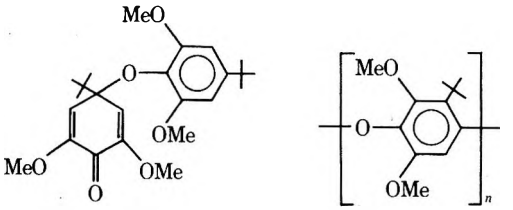
School of Forest Resources, North Carolina State University, Raleigh, North Carolina 27607

Received September 25, 1973

As part of a study of the alkaline oxidation of lignin[2] it was of interest to determine the nature of the products resulting from the oxidation of model phenols **1**, **2**, and **3** by one-electron-transfer reagents such as potassium ferricyanide, lead dioxide, silver oxide, etc. The products of such oxidations are usually dimers and oligomers formed by the coupling of intermediate phenoxy radicals[3] and, indeed, phenol **1** is known to give the quinol ether **4** on treatment with potassium ferricyanide or silver oxide.[4] We found compound **2** to behave in a similar manner, giving, on oxidation by ferricyanide in a benzene–aqueous potassium hydroxide system, an 85% yield of the polyphenylene ether **5** (mol wt *ca.* 2900). The polymer **5**, like **4**, was formed by coupling of the initially produced phenoxy radicals.



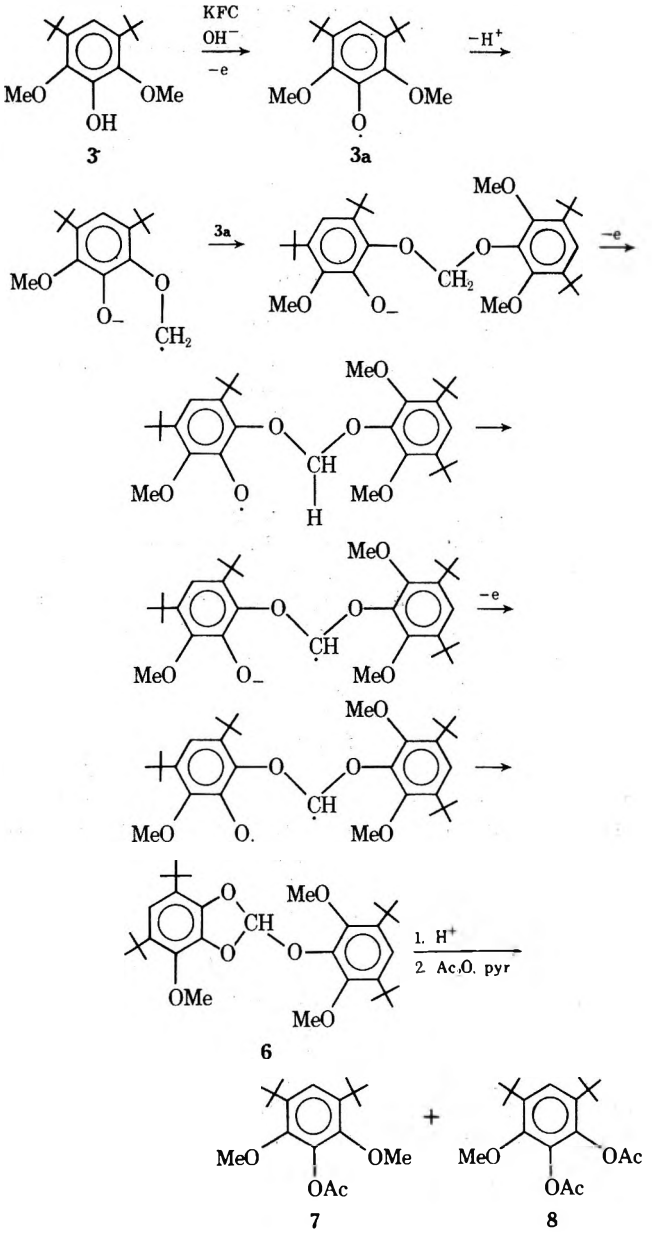
1 2 3



4 5

Phenol **3** reacted sluggishly under the same conditions and, although the benzene layer showed the intense emer-

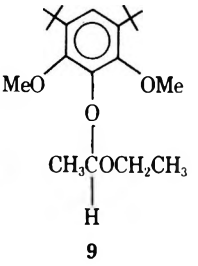
ald green color characteristic of 2,6-dimethoxy-substituted phenoxy radicals,[5] only a few per cent of **3** was altered after 5 hr at room temperature. However, at 70° phenol **3** was in 5 hr completely converted to a complex mixture of products, only one of which was present in significant quantity (26%). This product was characterized as the orthoformate **6** on the basis of analytical and spectral data (see Experimental Section). The structural assignment was confirmed by mild acid hydrolysis of **6** followed by acetylation of the reaction mixture to give the expected phenol acetate **7** (90%), identified by comparison with authentic samples obtained by acetylation of phenol **3**, and catechol diacetate **8** (76%), identified by analytical and spectral data.



This formation of the orthoformate represents a course of reaction which to our knowledge has not previously been reported in the area of phenol oxidation. Coupling between two molecules of phenol has occurred, but not in the usual manner where two mesomeric forms of a phenoxy radical couple with each other. Rather, coupling has occurred between one phenoxy radical and one secondarily formed radical at a methoxyl carbon of another phenol molecule. The same process occurs a second time, albeit intramolecularly, resulting in closure of the five-membered ring.

Apparently, this behavior is due to the bulkiness of the *tert*-butyl groups and probably methoxyl groups as well, which hinder the coupling of one phenoxy radical with an annular position on another. Thus, the reaction follows the normally unfavorable course of hydrogen abstraction from a neighboring methoxyl group, forming a radical which is sufficiently unhindered to couple with a phenoxy radical.

This explanation was further substantiated by repeating the oxidation with lead dioxide, using diethyl ether as solvent instead of benzene. The acetal **9** was isolated in 56% yield, demonstrating the ability of the phenoxy radical to abstract a secondary hydrogen atom from the ether and then couple with this radical. No orthoformate (**6**) was detected by tlc, reflecting as expected the preference for hydrogen abstraction from a secondary carbon, the ether, as opposed to a primary carbon, the methoxyl group, although the much larger concentration of diethyl ether in the reaction mixture undoubtedly also contributes to the overwhelming formation of acetal **9**.



9

Experimental Section

General. Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra (ir) were obtained on a Perkin-Elmer Model 521 infrared spectrophotometer. Ultraviolet (uv) and visible spectra were obtained with a Cary Model 15 ultraviolet–visible spectrophotometer. Nuclear magnetic resonance (nmr) spectra were obtained with a Varian Associates Model HA-100 spectrometer using chloroform-*d* as solvent and tetramethysilane as an internal reference. Mass spectra were obtained using either an AEI MS-12 or an AEI MS-902 double-focusing spectrometer. Elemental analyses were performed by Atlantic Microlab, Inc., Atlanta, Ga.

3-*tert*-Butyl-2,6-dimethoxyphenol (2). A petroleum ether (bp 80–110°) solution containing 10.0 g (0.065 mol) of 2,6-dimethoxyphenol and 11.0 g (0.15 mol) of *tert*-butyl alcohol was stirred vigorously and heated to 50°. To this solution, 2 ml of concentrated sulfuric acid was added dropwise over a 0.5-hr period and the reaction solution was then maintained at 50° for another 2.5 hr. After cooling, the reaction mixture was washed twice with 50-ml portions of water, dried over sodium sulfate, and concentrated under reduced pressure.

The residue was placed on a 5.0 × 25.0 cm column of Grace activated silica gel (100–200 mesh) and eluted with benzene. Evaporation of the collected benzene fraction gave 6.20 g (46%) of 3-*tert*-butyl-2,6-dimethoxyphenol: mp 52–53° from 95% ethanol; nmr δ 1.32 (9 H, s, *tert*-butyl), 3.79 (3 H, s, methoxyl), 3.90 (3 H, s, methoxyl), 5.50 (1 H, s, phenolic hydroxyl), 6.50 (1 H, d, J = 9.0 Hz, aromatic), 6.74 (1 H, d, J = 9.0 Hz, aromatic).

Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.57; H, 8.57. Found: C, 68.54; H, 8.61.

3,5-Di-*tert*-butyl-2,6-dimethoxyphenol (3). To a 100-ml three-necked flask equipped with a condenser and a bubble tube were added 7.0 g (0.045 mol) of 2,6-dimethoxyphenol and 12 ml of benzene. This mixture was heated to reflux and isobutylene was bubbled in throughout the entire reaction. Under vigorous stirring, a total of 1 ml of concentrated sulfuric acid was added dropwise over the first 2 hr of reaction. After addition of the sulfuric acid, refluxing was continued for 4.5 hr.

Upon cooling, the desired compound began to crystallize from solution; therefore the reaction mixture was diluted with 100 ml of benzene, washed with two 50-ml portions of water, and dried over sodium sulfate. The benzene was removed under vacuum to leave a residue of crystals and some oil. Recrystallization of the residue from 95% ethanol yielded 6.40 g (53%) of 3,5-di-*tert*-butyl-

2,6-dimethoxyphenol: mp 138–139.5°; nmr δ 1.35 (18 H, s, two *tert*-butyl), 3.84 (6 H, s, two methoxyl), 5.26 (1 H, s, phenolic hydroxyl), 6.79 (1 H, s, aromatic).

Anal. Calcd for $C_{16}H_{26}O_3$: C, 72.18; H, 9.77. Found: C, 72.15; H, 9.82.

Oxidation of 3-*tert*-Butyl-2,6-dimethoxyphenol (2) with Alkaline Potassium Ferricyanide. A solution of 1.20 g of the phenol 2 in 75 ml of benzene was stirred vigorously with a solution of 6.00 g of potassium ferricyanide and 5.60 g of potassium hydroxide in 50 ml of water at 25° for 5 hr. The benzene solution was washed twice with water, dried over sodium sulfate, and evaporated to dryness, and the residue was taken up in chloroform and precipitated with methanol. The precipitate was filtered and dissolved and reprecipitated twice more to give 1.01 g (*ca.* 85%) of the polyphenylene polymer **5**.

The lightly cream colored polymer softened and melted over the range 140–160°. The osmometrically determined molecular weight was 2923 using chloroform as solvent and measurements at three different concentrations. The ir (KBr) showed the following major peaks: 2950 (s), 1595 (s), 1480 (s), 1435 (s), 1383 (s), 1200 (s), 1108 (s), 1060 cm^{-1} (s). The nmr showed peaks at δ 1.57 (s, *tert*-butyl), 3.37 and 3.74 (both s, two different methoxyls), and 5.95 (s, aromatic) in the approximate ratio 9:3:3:1, respectively. One further small peak at δ 1.35 is probably due to the *tert*-butyl group on the terminal unit of the polymer. None of these peaks disappeared upon the addition of deuterium oxide to the sample.

Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.23; H, 7.69. Found: C, 68.47; H, 7.65.

Oxidation of 3,5-Di-*tert*-butyl-2,6-dimethoxyphenol (3) with Alkaline Potassium Ferricyanide. A solution of 1.20 g of the phenol in 75 ml of benzene was stirred vigorously with a solution of 6.00 g of potassium ferricyanide and 5.60 g of potassium hydroxide in 50 ml of water at 70° for 5 hr. The benzene solution was washed twice with water, dried over sodium sulfate, and evaporated to dryness. The residue, a red-brown oil, was dissolved in 8 ml of acetone and allowed to stand in the refrigerator overnight. The precipitated product was filtered and the filtrate was diluted with 15 ml of 95% ethanol and filtered again to remove the second batch of precipitate. The combined precipitates were recrystallized from acetone to give 0.318 g (26%) of the orthoformate **6**: mp 152–153°; ir (KBr) 2960 (s), 1595 (w), 1485 (s), 1418 (s), 04 (s), 1358 (m), 1300 (m), 1230 (s), 1105 (s), 1070 (s), 1008 (s), 990 cm^{-1} (s); nmr δ 1.32 (36 H, narrowly split d, four *tert*-butyl), 3.80 (6 H, s, two methoxyl), 3.96 (3 H, s, methoxyl), 6.77 (1 H, s, trioxymethine), 7.03 (2 H, s, aromatic); none of these peaks disappears upon addition of deuterium oxide to the sample; nuclidic mass, 528.3389 (calcd for $C_{32}H_{48}O_6$, 528.3450); mass spectrum *m/e* (rel intensity) 528 (2.7), 513 (1.0), 266 (1.5), 265 (2.7), 264 (18.8), 263 (100.0), 251 (3.6).

Anal. Calcd for $C_{32}H_{48}O_6$: C, 72.85; H, 9.10. Found: C, 72.67; H, 9.10.

The structure of the orthoformate was confirmed by hydrolysis and subsequent acetylation of the products. Thus, 0.280 g of orthoformate was hydrolyzed in 20 ml of 95% ethanol–chloroform (1:1) containing 5 drops of concentrated hydrochloric acid. The solution was warmed on a steam bath for 1 hr and diluted with water, and the chloroform layer was removed. After drying over sodium sulfate, the chloroform was removed and the residue was acetylated with pyridine–acetic anhydride (1:1). After 24 hr the volatiles were removed under vacuum and ptlc of the residue using benzene–hexane (1:1) gave 0.127 g (76%) of the catechol diacetate **8** and 0.149 g (90%) of the phenol acetate **7**.

The phenol acetate, mp 144–145° from hexane, was identified by comparison of its melting point, mixture melting point, and ir with those of authentic material which was obtained by acetylation of phenol **3**.

Anal. Calcd for $C_{18}H_{28}O_4$: C, 70.10; H, 9.10. Found: C, 70.08; H, 9.19.

The catechol diacetate had mp 130–132° from hexane; ir (KBr) 2960 (m), 1770 (s), 1410 (s), 1200 (s), 1155 (s), 1062 cm^{-1} (s); nmr δ 1.27 and 1.32 (9 H each, both s, two *tert*-butyl), 2.22 and 2.24 (3 H each, both s, two acetyl), 3.77 (3 H, s, methoxyl), 7.21 (1 H, s, aromatic).

Anal. Calcd for $C_{19}H_{28}O_5$: C, 67.90; H, 8.34. Found: C, 68.01; H, 8.31.

Oxidation of 3,5-Di-*tert*-butyl-2,6-dimethoxyphenol (3) with Lead Dioxide in Ether. To a vigorously stirred suspension of lead dioxide (5.0 g) in 100 ml of dry diethyl ether, 2.45 g of the phenol was added. The reaction mixture was maintained at 25° for 4 hr and then filtered to remove the lead dioxide. The solution was washed with two 50-ml portions of water, dried over sodium sulfate, and evaporated to dryness. After tlc on silica gel using benzene–hexane (1:1), a compound was obtained as a partially crystallized oil. The oil was vacuum distilled to give 1.40 g (*ca.* 56%) of the acetal **9** which crystallized in the receiver: mp 36.3°; nmr δ 1.01 (3 H, t, methyl), 1.29 (18 H, s, *tert*-butyl), 1.44 (3 H, d, J = 5 Hz, methyl), 3.49 (2 H, m, methylene), 3.84 (6 H, s, methoxyl), 5.24 (1 H, q, J = 5 Hz, acetal), 6.94 (1 H, s, aromatic); mass spectrum *m/e* 338 (molecular ion), 266, 251, 235, 221, 166, 73, 45.

Anal. Calcd for $C_{20}H_{34}O_4$: C, 71.00; H, 10.07. Found: C, 71.16; H, 10.04.

Registry No.—**2**, 49746-11-4; **3**, 49746-12-5; **5**, 50322-12-8; **6**, 49746-13-6; **8**, 49746-14-7; **9**, 49746-15-8; 2,6-dimethoxyphenol, 91-10-1.

References and Notes

(1) (a) Former graduate student, Department of Wood and Paper Science, North Carolina State University; (b) Associate Professor of Wood and Paper Science; (c) Professor of Chemistry.
(2) R. C. Eckert, H-m. Chang, and W. P. Tucker, *Tappi*, **56** (6), 134 (1973).
(3) H. Musso in "Oxidative Coupling of Phenols," W. I. Taylor and A. R. Battersby, Ed., Marcel Dekker, New York, N. Y., 1967, pp 1–82.
(4) C. J. R. Adderley and F. R. Hewgill, *J. Chem. Soc. C*, 1438 (1968).
(5) C. Steelink, *Advan. Chem. Ser.*, **59**, 51 (1966).

A Facile Synthesis of 2-Aminonicotinaldehyde

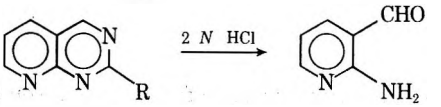
Thomas G. Majewicz and Paul Caluwe*

State University of New York, Polymer Research Center, College of Environmental Science and Forestry, Syracuse, New York 13210

Received September 24, 1973

Aromatic o-aminoaldehydes are valuable starting materials for a wide variety of N-heterocyclic compounds. However, in spite of their seemingly simple array of functionality, they are difficult to synthesize and in fact relatively few compounds possessing this pair of functions have been described. In connection with our investigation of the Friedländer condensation as a synthetic method for the linear annellation of pyridine rings, large quantities of 2-aminonicotinaldehyde (**2**) were required.

The preparation of **2** had previously been accomplished by a multistep synthesis starting from 2-amino-3-picoline,[1,2] but this proved to be a tedious procedure with substantial loss of material upon purification. Therefore, an alternate route to **2** was sought. An attractive possibility was to employ the pyrimidine moiety of pyrido[2,3-*d*]pyrimidine (**1a**) as a source for the o-aminoaldehyde functionality. Covalent hydration of this heterocyclic system makes it susceptible to hydrolytic ring opening of the pyrimidine nucleus.[3] This reaction is of no synthetic value, since **1a** was synthesized from **2**.[3] However, sulfamation of nicotinamide with ammonium sulfamate[4] readily provided us with 2-(3′-pyridyl)pyrido[2,3-*d*]pyrimidine (**1b**) in 50% yield together with nicotinonitrile.



1a, R = H
b, R = 3-pyridyl

2

As anticipated, hydrolysis of this crude reaction mixture in 2 *N* HCl gave **2** and nicotinic acid. Separation was readily accomplished by extraction with ether, yielding pure **2** in 50% yield (based on nicotinamide). Proof of structure was obtained by spectroscopic data, by comparison with an authentic sample,[1] and by its conversion into derivatives of 1,8-naphthyridine by Friedländer condensation.[5]

Finally, it should be noted that the o-aminoaldehyde functionality in 2 is generated in one single reaction step, in contrast with previous routes to aromatic o-aminoaldehydes, where both functional groups are elaborated separately.

Experimental Section

A mixture of nicotinamide (36.5 g, 0.3 mol) and ammonium sulfamate[4] (52 g, 0.45 mol) was heated in an oil bath at 150°. After a clear melt was obtained, the temperature was raised slowly to 200°. The mixture was kept at this temperature for 6 hr, after which the content of the flask had completely solidified. Water was added and the precipitate collected and washed with ether to remove nicotinonitrile. The solid material thus obtained[6] was refluxed in 2 *N* HCl for 4 hr, made alkaline and extracted with ether. The resulting ether solution was dried (K_2CO_3) and evaporated to give pure 2-aminonicotinaldehyde (2) (9 g, 50%): mp 98–99° (lit.[2] 98°); ir (Nujol) 3440, 3250, 3125, 2750, 1650. 1625, 1575, 1540 cm^{-1}; nmr δ_{TMS} (DMSO-d_6) 9.96 (s, 1, HCO), 8.33 (dd, 1, H-α, $J_{\alpha-\beta}$ = 4 Hz, $J_{\alpha-\gamma}$ = 2 Hz), 8.08 (dd, 1, H-γ, $J_{\beta-\gamma}$ = 8 Hz), 7.6 (broad, 2, NH_2), 6.8 (dd, 1, H-β).

Acknowledgment. This research was sponsored in part by the U. S. Army Research Office, Durham, N. C. We thank Mr. R. Hart for carrying out some preliminary experiments.

Registry No.—2, 7521-41-7; nicotinamide, 98-92-0; ammonium sulfamate, 7773-06-0.

References and Notes

(1) V. Oakes, R. Pascoe, and H. N. Rydon, *J. Chem. Soc.*, 1045 (1956).
(2) A. Albert and F. Reich, *J. Chem. Soc.*, 1372 (1960).
(3) W. L. F. Armarego, *J. Chem. Soc.*, 4094 (1962).
(4) J. P. Osselaere, J. V. Dejardin, and M. Dejardin-Duchêne, *Bull. Soc. Chim. Belg.*, **78**, 289 (1969).
(5) (a) T. G. Majewicz and P. Caluwe, to be submitted for publication. (b) E. M. Hawes and D. G. Wibberley, *J. Chem. Soc. C*, 315 (1966).
(6) Purification of this material had no beneficial effect on the yield and purity of the final product. Its recrystallization from water gave pure **1b** (15.6 g, 50%), mp 224.

Enthalpy of the Diels–Alder Reaction of Cyclopentadiene and Maleic Anhydride

Kenneth J. Breslauer and David S. Kabakoff*

Department of Chemistry, Yale University, New Haven, Connecticut 06520

Received September 7, 1973

In connection with a program of research on the energetics of cycloaddition reactions, we determined the enthalpy of the reaction between cyclopentadiene (CPD) and maleic anhydride (MA). Our report is prompted by the recent publication of similar data by Rogers and Quan.[1] These workers determined the heat for the DA reaction by standard solution calorimetric techniques. While the literature of thermal reactions abounds with kinetic data, measurement of enthalpies of reaction lags far behind. Where such data exist, they are often derived indirectly from heats of combustion or hydrogenation, or from van't Hoff data.[2] Our measurements provide an example of an application of flow calorimetry to the study of an organic reaction in solution.

The flow calorimeter and method employed have been described by Sturtevant.[3] The main components of the apparatus are a precision fluid delivery system capable of a wide range of delivery rates, a thermopile, and a massive aluminum heat sink. The reactant solutions are preequilibrated to the desired temperature and delivered through separate tubes to a junction where they are mixed just as they reach the thermopile. The heat evolved or absorbed upon mixing the solutions is quantitatively conducted through the thermopile to the heat sink. The output of the thermopile is integrated to yield the total heat transferred during a specified period.

Table I
Enthalpy of the Reaction of CPD and MA in Dioxane

Temp, °C	Run	CPD flow rate[a]	MA flow rate[a]	$-\Delta H_1$[b]
25.0	1[c]	2.8	2.8	24.14
	2	2.8	1.4	24.50
	3	2.8	1.0	24.56
	4[d]	2.0	2.0	24.92
	5	2.8	2.8	25.37
	6	1.4	1.4	24.27
	7	2.0	2.0	25.19
	8	2.8	2.8	25.24
	Average			24.8 ± 0.5[e]
40.0	1[f]	1.4	1.4	25.50
	2	2.0	2.0	25.59
	3	2.8	2.8	25.77
	4	2.0	1.4	25.62
	5	2.8	1.4	25.69
	6	1.4	2.0	25.36
	7[g]	1.4	1.4	25.78
	8	2.0	2.0	25.40
	9	2.8	2.8	25.39
	10	2.0	1.4	25.74
	11	2.8	1.4	25.45
	12	1.4	2.0	24.90
	Average			25.5 ± 0.3[e]

[a] A relative flow rate of 1 is 3.53 ml/min. [b] Kcal/mol. [c] Runs 1–3: [CPD] = 1.06×10^{-1} *M*; [MA] = 2.0×10^{-1} *M*. [d] Runs 4–8: [CPD] = 2.12×10^{-1} *M*; [MA] = 4.0×10^{-1} *M*. [e] The error is the standard deviation. [f] Runs 1–5: [CPD] = 1.88×10^{-1} *M*; [MA] = 4.0×10^{-1} *M*. [g] Runs 7–12: [CPD] = 1.98×10^{-1} *M*; [MA] = 4.0×10^{-1} *M*.

In the experiments performed, solutions of CPD ($1–2 \times 10^{-1}$ *M*)[4] and MA ($2–4 \times 10^{-1}$ *M*) in dioxane were allowed to react in the calorimeter. Upon mixing, an exothermic reaction ensued and the thermopile output increased to a steady-state value. The heat evolution was integrated for at least 5 min of the steady-state period. It should be noted that the flow rates of the two reactants were varied relative to one another, in order to demonstrate that the reaction was complete during the residence time in the calorimeter. Experiments were performed at 25 and 40°. The results of multiple runs are summarized in Table I. Control experiments indicated that there was negligible heat change on mixing of pure dioxane, or of dioxane with either reactant solution.

The enthalpy of reaction of CPD and MA in dioxane solution was found to be −24.8 ± 0.5 kcal/mol at 25.0°, and −25.5 ± 0.3 kcal/mol at 40° (the error quoted is the standard deviation). The precision of our values is not high enough to permit conclusions about the ΔC_P of this reaction, except to say that this term is probably small.

Comparison of our value of ΔH_r (25°) = −24.8 ± 0.5 kcal/mol for the reaction in dioxane and the value of Rogers and Quan of ΔH_r (25°) = −26.2 ± 0.1 kcal/mol for the reaction in dichloromethane indicates very good agreement after correction for solvent effects. Most of the data needed for solvent-effect corrections can be found in the work of Haberfield and Ray[5] as well as that of Rogers and Quan. The latter two investigators determined the heats of solution of CPD, MA, and the product *endo*-5-norbornene 2,3-dicarboxylic anhydride (N) in CH_2Cl_2.[6] The heat of solution of CPD in CH_2Cl_2 is 0.1 kcal/mol. This quantity is unknown in dioxane but it is almost certainly small, and can be assumed to be equal to the value in CH_2Cl_2 as a first approximation. The heat of solution of MA in dioxane is also known from the work of Haberfield and Ray.[5]

The enthalpy of transfer of the reactants from dioxane to CH_2Cl_2, $\delta\Delta H_{soln}$ (reactants) = ΔH^r_{soln} (CH_2Cl_2) − ΔH^r_{soln} (dioxane), is 1.2 kcal/mol. The heat of solution of N in dioxane is unknown. If it is assumed to be equal to the value in CH_2Cl_2, the small difference between our value and that of Rogers and Quan reduces to 0.3 kcal/mol, which is well within experimental error. Even if one assumes a value as large as 1 kcal/mol for the enthalpy of transfer of the product from dioxane to CH_2Cl_2, one would still find that our results are in good agreement with the values determined by standard solution calorimetry.[7]

In conclusion, we wish to emphasize that the flow calorimetric method employed is fast, convenient, and requires small amounts of sample. It is potentially applicable to measurement of enthalpies of a wide variety of fast organic reactions in solution.

Experimental Section

Materials. Maleic anhydride (Eastman Organic Chemicals) was recrystallized from $CHCl_3$, sublimed under vacuum, and stored in a desiccator until use. Dioxane was purified by refluxing over sodium followed by distillation (onto molecular sieves) immediately before use. CPD was obtained by cracking *endo*-dicyclopentadiene which had been purified by the method of Harkness, *et al.*[10]

Calorimetry. The flow calorimeter (a modified Beckman Model 190 microcalorimeter) has been described in detail elsewhere.[3,11] Calibration was accomplished by measuring the enthalpy of reaction of 1.000×10^{-3} *N* HCl and 2.000×10^{-3} *N* NaOH, employing the values given by Grenthe, *et al.*,[12] for the enthalpy of formation of water.

The temperature of the calorimeter was regulated to within ±0.005° at both temperatures at which the reaction was investigated. The output of the thermopile during the steady-state period was integrated using a ball and disk integrator. The integration precision is estimated to be better than ±1%.

Acknowledgment. We thank Professor Julian M. Sturtevant for the use of his flow calorimeter. David Kabakoff wishes to thank the National Institutes of Health for a predoctoral fellowship (Number GM-47, 980-03). This work was supported, in part, by grants from the National Science Foundation, GP-33909X to Professor Jerome A. Berson, and GB-36346X to Professor Sturtevant. We thank Professor Berson for his encouragement.

Registry No. CPD, 542-92-7; MA, 108-31-6.

References and Notes

(1) F. E. Rogers and S. W. Quan, *J. Phys. Chem.*, **77**, 828 (1973).
(2) K. B. Wiberg in "Determination of Organic Structures by Physical Methods," Vol. 3, Academic Press, New York, N. Y., 1971, Chapter 4.
(3) (a) J. M. Sturtevant and P. A. Lyons, *J. Chem. Thermodynamics*, **1**, 201 (1969); (b) S. F. Velick, J. P. Baggott, and J. M. Sturtevant, *Biochemistry*, **10**, 779 (1971).
(4) At these concentrations negligible dimerization of CPD occurred.
(5) P. Haberfield and A. K. Ray, *J. Org. Chem.*, **37**, 3093 (1972).
(6) A reviewer has questioned whether the product is 100% endo adduct. Although we did not determine this, the paper by Rogers and Quan[1] states that "Wilder and Gratz fractionally crystallized a kinetically determined reaction mixture and found 1.4% exo." The citation to the above experiment is erroneous, neither has this work been done by P. Wilder, Jr. (private communication). We have been unable to find the source of the report; however, even if it is substantiated, the enthalpy difference between N and X is expected to be quite small, so that the effect on our measured enthalpy is negligible.
(7) Using their data Rogers and Quan calculated a value for $\Delta H_r(g)$, and suggested an empirical equation for estimation of the heat of any DA reaction

$$\Delta H_r^d(g) - \Delta H_r^e(g) = \Delta H_H^d - \Delta H_H^e \quad (1)$$

where $\Delta H_r^d(g)$ is the heat of addition of any diene to dienophile (d), $\Delta H_r^e(g)$ is the enthalpy of addition to ethylene, and ΔH_H^d and ΔH_H^e are the heats of hydrogenation of the dienophile and ethylene. Applying this equation to the reaction of CPD + MA they calculated a value for $\Delta H_r(g)$ which was 2.6 kcal/mol less exothermic than the experimental value. It should be noted that the value of $\Delta H_r^e(g)$ is derived from the heat of formation of norbornene. The value used by Rogers and Quan of 20.6 kcal/mol has been updated by the work of Hall, *et al.*,[8] who find ΔH°_f (norbornene) = 15.1 kcal/mol. The calculated value according to eq 1 should therefore be higher than the experimental value by 2.9 kcal/mol. In addition, their conclusion that the strain energy of N contains only a small contribution from the succinic anhydride moiety (1.1 kcal/mol) now seems to be incorrect, in view of the new value for strain energy (SE) of norbornene (17.6 kcal/mol), and a revised value (4.5 kcal) for the strain contribution of a succinic anhydride moiety recently published by Eigenmann, Golden, and Benson.[9] Using the revised group additivity parameters for enthalpies of formation of oxygen-containing compounds,[9] we calculate $\Delta H_f(g)$ (N) = −111.8 kcal/mol. Comparing this value with the experimental value of −89.8 kcal/mol, the strain energy in N is 22 kcal/mol. [Note: SE (norbornene) + SE (succinic anhydride) = 22.1 kcal/mol].
(8) H. K. Hall, Jr. C. D. Smith, and J. H. Baldt, *J. Amer. Chem. Soc.*, **95**, 3197 (1973).
(9) H. K. Eigenmann, D. M. Golden, and S. W. Benson, *J. Phys. Chem.*, **77**, 1687 (1973).
(10) J. B. Harkness, G. B. Kistiakowsky, and W. H. Mears, *J. Phys. Chem.*, **5**, 682 (1937).
(11) K. J. Breslauer, Ph.D. Thesis, Yale University, 1973.
(12) I. Grenthe, H. Ots, and O. Ginshrup, *Acta Chem. Scand.* **24**, 1067 (1970).

Reaction of *N*-Iodosuccinimide with Secondary Alcohols

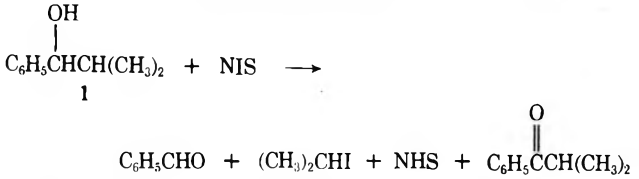
Thomas R. Beebe,* Alex L. Lin, and Robert D. Miller

Department of Chemistry, Berea College, Berea, Kentucky 40403

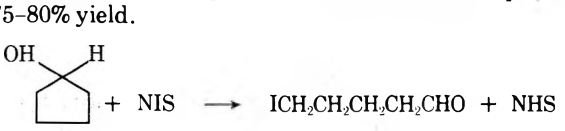
Received July 3, 1973

The reaction of tertiary alcohols with *N*-iodosuccinimide (NIS) has been shown to produce alkyl iodides and ketones.[1] The two products give good evidence that an alkyl hypoiodite is an intermediate in the reaction. The small number of secondary alcohols that have been oxidized with NIS produce ketones[2] and cyclic ethers.[3] The formation of a cyclic ether from a secondary alcohol and NIS suggests that an intermediate hypoiodite is probably formed (Barton-type reaction), while the production of a ketone may involve either hypoiodite formation or succinimidyl radical hydrogen abstraction.[2]

To gain more evidence for the general mechanistic pathway involved in the oxidation of secondary alcohols with NIS, NIS was allowed to react with three secondary alcohols, 2-methyl-1-phenyl-1-propanol (**1**, Table I), cyclopentanol (2), and 2,6-dimethyl-4-heptanol (3), that we believed would not form ketones if an intermediate hypoiodite was involved in the oxidation. Two of the secondary alcohols had previously been oxidized with reagents that are thought to produce hypohalite intermediates, and ketones were not the major product. Cyclopentanol gives 5-iodopentanal when treated with iodine and mercuric oxide in carbon tetrachloride[4] and 2,6-dimethyl-4-heptanol gives a furan when treated with bromine and silver acetate.[5]



The reaction of 1 with NIS in carbon tetrachloride at reflux in the presence of visible light[6] produced 78–87% benzaldehyde and 4–12% isobutyrophenone.[7] The 2-iodopropane product was found to be produced in 83% yield when no solvent was present. Succinimide was produced in 75–80% yield.



Scheme I

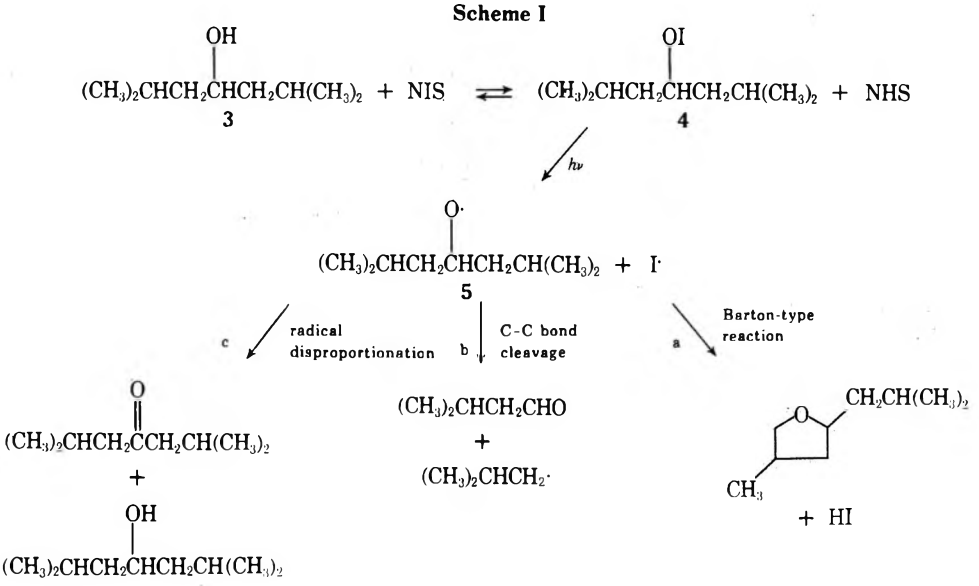
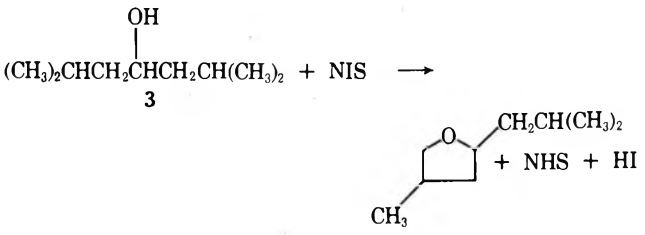


Table I
Oxidation of 2-Methyl-1-phenyl-1-propanol with NIS

Conditions (solvent, irradiation, time)	Yield of products, % Benzaldehyde	Isobutyrophenone
CCl_4, $h\nu$, 2 hr	84	4
CCl_4, dark, 4 hr	87	5
CCl_4, $h\nu$, 3 hr	78	7
CCl_4, $h\nu$, 3 hr	80	12
No solvent, $h\nu$, 2 hr[a]	88	7

[a] The 2-iodopropane peak was not separated on the vpc from the carbon tetrachloride solvent peak. When 2-methyl-1-phenyl-1-propanol was oxidized with NIS with no solvent present 2-iodopropane was found in a yield of 83%.

Irradiation of **2** with NIS in carbon tetrachloride at reflux produced 5-iodopentanal. The 5-indopentanal was isolated as a 2,4-dinitrophenylhydrazone derivative in 15–25% yields. An nmr spectrum ($CDCl_3$) of the crude aldehyde produced triplets at δ 9.61 (CHO) and 3.27 (ICH_2) and a complex multiplet at δ 1.6–2.0 (CH_2). An ir spectrum gave characteristic[8] aldehyde C–H stretching vibrations at 2747 and 2890 cm^{-1} and a carbonyl band at 1754 cm^{-1}. Analyses of the crude aldehyde by vpc showed only trace amounts of cyclopentanone.



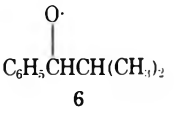
When **3** was treated at reflux with NIS in carbon tetrachloride, 35–40% of the cyclic ether (3-methyl-1-isobutyltetrahydrofuran) was produced with only 3–5% formation of the corresponding ketone. Small amounts (2–3%) of the C–C cleavage products, 2-methyl-1-iodopropane and 3-methylbutanal, were also found.

An nmr analysis of the ether, isolated from the vpc, produced overlapping doublets (δ 0.85, 0.96, 1.09, 9 H, 3 CH_3) and complex multiplets (δ 3.1–4.2, 3 H, 1 CH_2O and 1 CHO and δ 1.2–2.4, 6 H, 2 CH_2 and 2 CH). The mass spectrum of the ether included peaks with m/e 142 (M^+) and 85. Infrared analysis of the ether showed an absence of both carbonyl and hydroxyl peaks.

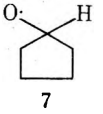
The products formed from the reaction of the above three alcohols with NIS suggest that a hypoiodite intermediate is formed, possibly in an equilibrium step. (Barton and his coworkers[9] have prepared *N*-iodoamides with *tert*-butyl hypoiodite.) An example of the proposed reaction pathway is given in Scheme I using **3** as the alcohol oxidized with NIS.

Once the hypoiodite is formed, visible light homolytically cleaves the O–I bond to produce the *sec*-alkoxy radical **5**, which has several decomposition pathways available to it. The Barton-type reaction (route a) is the preferred decomposition route for this *sec*-alkoxy radical, while a small percentage of the radicals undergo C–C bond cleavage (route b). The small percentage of ketone occurs (route c) presumably by radical disproportionation[10] rather than by loss of a hydrogen atom or iodine atom hydrogen abstraction.

However, the *sec*-alkoxy radicals **6** and **7** do not have the Barton reaction available to them and their decompositions follow a route similar to pathway b, C–C bond cleavage.



6



7

The products formed from the reaction of NIS with the three secondary alcohols studied indicate that an alkyl hypoiodite is probably formed as an intermediate. The alkyl hypoiodite then decomposes to produce ethers, aldehydes, and alkyl iodides as major products. However, ketones are produced in small amounts. The mechanistic pathway for the formation of the ketones may involve the alkyl hypoiodite or it may involve hydrogen abstraction by the succinimidyl radical.

Experimental Section

Analyses were carried out using a Perkin-Elmer 810 vpc and a Varian Aerograph Model 700 vpc. Infrared analyses were done using a Perkin-Elmer 337 grating infrared spectrophotometer. Nuclear magnetic resonance spectra were determined using a Varian T-60. Irradiation of the reaction mixtures was effected with a G.E. Projector Spot 150-W, 130-V tungsten lamp. The NIS was purchased from K & K Laboratories and was not recrystallized. The alcohols, ketones, benzaldehyde, isopropyl iodide, and internal standards were purchased from Matheson Scientific and were fractionally distilled. Vpc analyses of the 1-phenyl-1-propanol and 2,6-dimethyl-4-heptanol reactions were performed using a

7% SE-30 and 1.5% Carbowax 20M 6-ft column. All reactions were run at reflux and were irradiated. The reactions were continued until the reaction mixture gave a negative test with starch–potassium iodide paper. A description of the oxidation of 2,6-dimethyl-4-heptanol with NIS is given in detail. The other two reactions were performed in a similar manner.

Reaction of 2,6-Dimethyl-4-heptanol with NIS. Four milliliters of a CCl_4 solution containing 2,6-dimethyl-4-heptanol (1.57 mmol) and bromobenzene (0.93 mmol) was added to a 10-ml pear-shaped flask. To this solution was added 0.182 g (0.809 mmol) of NIS. The mixture was irradiated, heated at reflux, and stirred for 6 hr. Vpc analyses indicated a 39% yield of 3-methyl-1-isobutyltetrahydrofuran, a 3% yield of 2,6-dimethyl-4-heptanone, and 2% yields of 2-methyl-1-iodopropane and 3-methylbutanal.

Two reactions (with silver acetate added to reduce the decomposition of NIS by HI) produced 42 and 45% yields of the tetrahydrofuran product with the other products found in the 2–4% range. [The addition of silver acetate generally gave a small (5–7%) increase in the yield of tetrahydrofuran with no change in the percentage of the other products.]

Oxidation of Cyclopentanol with NIS. Five oxidations of cyclopentanol with NIS were performed. Vpc analyses of the reaction mixtures, after 3 hr, showed only trace amounts of cyclopentanone. The ω-iodopentanal was not found on the vpc. Evaporation of the CCl_4 solvent, after filtration of the reaction mixture, produced an oil. An nmr analysis of the oil showed a triplet at δ 9.61 (CHO) and 3.27 (ICH_2) and a complex multiplet at δ 1.6–2.0 ($CH_2CH_2CH_2$). A 2,4-dinitrophenylhydrazone derivative of the ω-iodoaldehyde gave a solid melting at 126–128°. (The 2,4-dinitrophenylhydrazone derivative[4] of the product obtained from the oxidation of cyclopentanol with HgO and I_2 melted at 127–128°.)

Acknowledgments. We thank The Research Corporation for generous support of this research. We also thank the University of Kentucky for nmr and mass spectrum analyses.

Registry No. 1, 611-69-8; **2,** 96-41-3; **3,** 108-82-7; NIS, 516-12-1.

References and Notes

(1) T. R. Beebe, M. Adkins, P. Kwok, and R. Roehm, *J. Org. Chem.*, **37**, 4220 (1972).
(2) T. R. Beebe and F. M. Howard, *J. Amer. Chem. Soc.*, **91**, 3379 (1969).
(3) K. Heusler, J. Kalvoda, C. Meystre, G. Anner, and A. Wettstein, *Helv. Chim. Acta*, **45**, 2162 (1962); K. Heusler, J. Kalvoda, P. Wieland, G. Anner, and A. Wettstein, *ibid.* **45**, 2575 (1962).
(4) M. Akhtar and D. H. R. Barton, *J. Amer. Chem. Soc.*, **86**, 1528 (1964); **83**, 2213 (1961).
(5) N. M. Roscher, *Chem. Commun.*, 474 (1971).
(6) Irradiation of the reaction mixtures was done with a G.E. Projector Spot 150-W, 130-V tungsten lamp.
(7) The expected isopropyl iodide was not found when the reactions were run in CCl_4, as the CCl_4 covered up the isopropyl iodide vpc peak. When a mixture of NIS and **1** was heated and irradiated without solvent, benzaldehyde and isopropyl iodide were both observed on the vpc.
(8) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," Wiley, New York, N. Y., 1959, p 156.
(9) D. H. R. Barton, A. L. J. Beckwith, and A. Goosen, *J. Chem. Soc.*, 181 (1965).
(10) P. Gray and A. Williams, *Chem. Rev.*, 59, 239 (1959).

Intramolecular C-2 → C-1 Hydrogen Transfer Reactions during the Conversion of Aldoses to 2-Furaldehydes[1,2a]

Donald W. Harris and Milton S. Feather*[2b]

Department of Agricultural Chemistry, University of Missouri, Columbia, Missouri 65201

Received July 27, 1973

Sugar 1,2-enediols have been suggested as intermediates in acid-catalyzed dehydration reactions and alkaline degradation reactions, as well as in the interconversion of aldoses and related 2-ketoses[3,4] (the Lobry de Bruyn–Alberda van Eckenstein transformation). In previous experiments designed to test the importance of 1,2-enediols and related enolic structures as intermediates in dehydration reactions, sugars were converted to 2-furaldehydes in acidified deuterium oxide or in tritiated water.[5] The finding that D-xylose is converted in acidified, tritiated water to 2-furaldehyde which is devoid of carbon-bound isotope[5] suggests that 1,2-enediols, if formed, further react immediately. Otherwise significant isotope incorporation would have been detected at the aldehyde carbon atom of 2-furaldehyde as a result of aldose–ketose interconversion. It has recently been found, however, that D-glucose is converted to D-fructose in acidic solution *via* a reaction involving an intramolecular transfer of hydrogen from C-2 of D-glucose to C-1 of D-fructose.[6,7] In strong acid (2 *N* sulfuric acid), the transfer appears to be complete and involves an isotope effect (K_h/K_t) of 4.3. Thus, in this case, the data are more consistent with a reaction mechanism involving an intramolecular C-2 → C-1 hydride transfer rather than the more generally accepted one involving a 1,2-enediol intermediate. These data suggest that aldose–ketose interconversion could easily have occurred, as a result of hydride transfer reactions, during dehydration reactions and remained undetected during isotope acquisition experiments.

The purpose of the present work was to evaluate the importance of C-2 → C-1 hydride transfers during some typical dehydration reactions. This was studied by preparing D-xylose and D-glucose specifically tritiated on C-2 and converting them to respectively 2-furaldehyde (I) and 5-(hydroxymethyl)-2-furaldehyde (II) in acidified water. A determination of the amount of carbon-bound tritium on the aldehyde carbon (which corresponds to C-1 of the original aldose) of I and II would provide information on the extent of C-2 → C-1 transfer occurring during the dehydration reactions and, in addition, provide qualitative information on the extent of aldose–ketose interconversion occurring during the dehydration reactions.

D-Glucose-2-^3H was prepared by converting D-fructose 6-phosphate to D-glucose 6-phosphate in tritiated water using phosphoglucose isomerase, followed by treating the resulting crystalline D-glucose 6-phosphate with alkaline phosphatase. This procedure was essentially the same as was used to prepare D-glucose-2-^2H.[8,9] That the D-glucose was tritiated only at C-2 is evident from the known[10,11] specificity of the enzyme, which produces, at equilibrium in tritiated water, only D-glucose-2-^3H 6-phosphate and D-fructose-*1*-^3H 6-phosphate, with no isotope being present at C-1 of the aldose. Further proof of this labeling specificty also observed in the past when the same procedure was used to prepare D-glucose-2-^2H,[8] which, from its nmr spectrum, was observed to be deuterated only at C-2. D-Xylose-2-^3H was prepared from D-glucose-2-^3H by converting the latter to 1,2-*O*-isopropylidene-D-glucofuranose followed by periodate oxidation to give 1,2-*O*-isopropylidene-D-xylo-1,5-dialdose-2-^3H. Reduction of the latter derivative with sodium borohydride gave 1,2-*O*-isopropylidene-D-xylofuranose-2-^3H, which was hydrolyzed to give chromatographically pure D-xylose-2-^3H.

D-Glucose-2-^3H was converted to II and a portion isolated as the crystalline bisether[12] oxybis(5-methylene-2-furaldehyde). The specific activity of the compound was 14% that of the starting sugar, indicating that each furan residue retained 7% of the radiochemical activity of the original D-glucose-2-^3H. A further portion of II was oxidized to 2-furoic acid which contained negligible activity indicating that all of the carbon-bound tritium was located on the aldehyde carbon of II. Considering the isotope effect involved for the conversion of D-glucose-2-^3H to D-fructose-*1*-^3H, approximately 30% of the dehydration reaction would involve hydride transfer if the reactant were protiated rather than tritiated.

D-Xylose-2-^3H was converted to I in acidified water in 33% yield. An aliquot of I was converted to the crystalline phenylhydrazone which contained 13% the activity of the starting sugar. Conversion of a further aliquot of I to 2-furoic acid which was radiochemically inert showed that all of the radiochemical activity was located on the aldehyde carbon of I.

The data collected established that intramolecular C-2 → C-1 hydrogen transfers occur during dehydration reactions, probably as a result of conversion of aldoses to ketoses as was established for the D-glucose to D-fructose conversion. It is noteworthy that analogous transfers in proceeding from 2-ketoses to aldoses have not yet been established in the case of chemical catalysis, and, for a complete assessment of the role and importance of reaction pathways involving intramolecular hydrogen shifts *vis-à-vis* 1,2-enediols, substantially more data will be required.

Experimental Section

Materials and Methods. Radiochemical activities were determined on a Packard Tri-Carb scintillation counter using a scintillant composed of two parts of a solution composed of 2 l. of toluene, 8.25 g of 2,5-diphenyloxazole (PPO), and 0.25 g of 1,4-bis-2-(4 methyl-5-phenyloxazole)benzene (Me_2POPOP), and one part of Triton X-100 (v/v). Ultraviolet spectra were obtained using a Coleman Model 124 recording double beam spectrophotometer. Thin-layer chromatography was performed using silica gel HF support with chloroform–methanol (95:5) as the eluent. Spots were visualized by uv light or by spraying with 10% ethanolic sulfuric acid followed by heating at 110° for 10 min. Paper chromatography was performed by the descending method using ethyl acetate–formic acid–acetic acid–water (18:1:3:4, v/v) as irrigant followed by visualization with aniline hydrogen phthalate spray reagent.[13] D-Glucose-2-^3H was prepared enzymatically as described in previous reports[6,7] and was diluted to a suitable level, as needed, with inert D-glucose, followed by recrystallization from water–ethanol.

Preparation of D-Xylose-2-^3H. D-Glucose-2-H (100 g, specific activity = 1.0 μCi/mmol) was converted to 1,2:5,6-di-*O*-isopropylidene-D-glucofuranose[14] (mp, mmp 108°) in 54% yield and then to 1,2-*O*-isopropylidene-D-glucofuranose,[14] which after recrystallization from ethyl acetate gave 25 g of material (mp, mmp 160°). This material was converted to syrupy 1,2-*O*-isopropylidene-D-xylo-1,5-dialdose-2-^3H by periodate oxidation,[15] and then reduced to 1,2-*O*-isopropylidene-D-xylofuranose with sodium borohydride.[15] The resulting syrupy material was dissolved in 100 ml of 0.1 *N* sulfuric acid and refluxed for 1 hr. After neutralization with barium carbonate, the resulting filtered solution was evaporated to dryness at reduced pressure to give a syrup which contained only D-xylose as evidenced by paper chromatography. To this syrup was added 5 g of inert D-xylose and sufficient water to produce a thick syrup, which slowly crystallized. The resulting crystalline D-xylose-2-^3H, which was isolated on a filter, washed with methanol, and dried *in vacuo*, had a specific activity of 2.42×10^{-2} μCi/mmol.

Conversion of D-Glucose-2-^3H to II. D-Glucose-2-^3H (200 g, specific activity = 0.916 μCi/mmol) was added to 2400 ml of 2 *N* sulfuric acid, and the solution was refluxed for 3.5 hr. The solution was extracted three times with chloroform and the extract was dried over anhydrous sodium sulfate and evaporated to dryness. The II contained by the residue was isolated by preparative thin-layer chromatography and identified by its chromatographic flow rate, which was identical with a standard sample, and from its uv spectrum (λ_{max} 278 mμ), which was identical with that of a standard sample. The overall yield of II was approximately 15 mg as determined from spectral measurements. Approximately half of this sample was converted to the oxybis(5-methylene-2-furaldehyde)[12] by heating at 100° for 2 hr. The resulting material (mp 113°) had a chromatographic flow rate and exhibited a uv spectrum identical with those of an authentic sample. This material, amounting to 5.7 mg, was counted and found to have a specific activity of 0.154 μCi/mmol. A further sample of II was converted to 5-(hydroxymethyl)-2-furoic acid,[8] which was purified by preparative thin-layer chromatography and had a thin-layer chromatographic flow rate and a uv spectrum identical with those of an authentic sample, amounted to 1.9 mg and had a specific activity of 8×10^{-3} μCi/mmol.

Conversion of D-Xylose-2-^3H to I. This conversion was made in 6 *N* sulfuric acid starting with 2.0 g of sugar (specific activity of 2.42×10^{-2} μCi/mmol) as described previously.[5] The 2-furaldehyde-^3H contained in 250 ml of distillate was identified by its ultraviolet spectrum which showed maxima at 227 and 278 mμ. Assuming a molar absorptivity of 16,000,[16] the absorbance at 278 mμ indicated a yield of 33%. The I in a 100-ml aliquot of the distillate was converted to 2-furaldehyde phenylhydrazone-^3H (mp, mmp 95°) which had a specific activity of 3.25×10^{-3} μCi/mmol. The I in a further 100 ml aliquot was converted to 2-furoic acid (mp, mmp 131°) which after purification by sublimation at 110° and 0.3 mm was found to be radiochemically inert.

Registry No.—I, 98-01-1; II, 67-47-0; D-xylose, 58-86-6; D-glucose, 50-99-7; 1,2:5,6-di-*O*-isopropylidene-D-glucofuranose, 582-52-5; 1,2-*O*-isopropylidene-D-glucofuranose, 18549-40-1; oxybis(5-methylene-2-furaldehyde), 7389-38-0; 2-furaldehyde phenylhydrazone, 2216-75-3; 2-furoic acid, 88-14-2.

References and Notes

(1) Journal Paper No. 6796 of the Missouri Agricultural Experiment Station.
(2) (a) Supported in part by grants from the Corn Refiners Association and the National Science Foundation Grant GP-38511. (b) To whom inquiries should be addressed.
(3) J. C. Speck, Jr., *Advan. Carbohyd. Chem.*, **13**, 63 (1958), and references therein.
(4) E. F. L. J. Anet, *Advan. Carbohyd. Chem.*, **19**, 181 (1964), and references therein.
(5) M. S. Feather, D. W. Harris and S. B. Nichols, *J. Org. Chem.*, **37**, 1606 (1972).
(6) D. W. Harris and M. S. Feather, *Tetrahedron Lett.*, 4813 (1972).
(7) D. W. Harris and M. S. Feather, *Carbohyd. Res.*, in press.
(8) M. S. Feather and J. F. Harris, *Carbohyd. Res.*, **15**, 304 (1970).
(9) Y. J. Topper, *J. Biol. Chem.*, **225**, 419 (1957).
(10) I. A. Rose and E. L. O'Connell, *Biochim. Biophys. Acta*, **42**, 159 (1960).
(11) I. A. Rose and E. L. O'Connell, *J. Biol. Chem.*, **236**, 3086 (1961).
(12) A. P. Dunlop and F. Peters, "The Furans," Wiley, New York, N. Y., 1953, p 411.
(13) S. M. Partridge, *Nature (London)*, **164**, 443 (1949).
(14) O. T. Schmidt in "Methods in Carbohydrate Chemistry," Vol. II, R. L. Whistler and M. L. Wolfrom, Ed., Academic Press, New York, N. Y., 1963, p 321.
(15) R. Schaffer and H. S. Isbell, *J. Res. Nat. Bur. Stand.*, **56**, 191 (1956).
(16) Reference 12, p 13.

Preparation and Characterization of Propiolyl Chloride

Walter J. Balfour,* Colin C. Greig, and Somyong Visaisouk

Department of Chemistry, University of Victoria, Victoria, British Columbia, Canada

Received September 10, 1973

Propiolyl chloride is the simplest of the acetylenic acid chlorides. We became interested in the compound, from the spectroscopic point of view, as part of a program to study the influence of conjugation and halogen substitution on the energies and stabilities of (π^*, n) electronic states. While unsuccessful attempts to prepare propiolyl chloride have been reported,[1] brief mention is made in the chemical patent literature of its use in dye and plastics manufacture.[2]

The present communication describes a straightforward synthesis from propiolic acid and phosphorus pentachloride. The major product of the reaction is identified as

$$HC{\equiv}CCOOH + PCl_5 \longrightarrow HC{\equiv}CCOCl + POCl_3 + HCl$$

propiolyl chloride from spectroscopic and chemical evidence. The boiling point of the propiolyl chloride prepared in this way does not correspond to that of a compound prepared by pyrolysis of α,β-dichloropropionyl chloride, and claimed by Schaefer[2b] to be propiolyl chloride. Our product boils at 58–60° while Schaefer reports a boiling point in the range 72–75°.

Experimental Section

Preparation. Propiolic acid (5 g, 0.07 mol) was added dropwise to a small excess of PCl_5 (16 g, 0.075 mol) at room temperature over 3–4 hr. In early experiments the resulting clear, pale yellow liquid was fractionally distilled at atmospheric pressure through a 10-cm packed glass column, when a lachrymatory liquid, subsequently characterized as propiolyl chloride, distilled at 58–60°. However, on several occasions the sample so obtained ignited spontaneously on exposure to air. On the assumption that this behavior was due to trace amounts of monochloroacetylene,[3] formed by thermal decomposition during distillation, purification was subsequently effected without heating. The reaction mixture, cooled to liquid nitrogen temperature, was allowed to warm up. On warming, the volatile components were pumped off through two cold traps, the first at *ca.* −78°, the second at *ca.* −135°. The trap at *ca.* −78° effectively removed all the $POCl_3$ produced and propiolyl chloride was collected in the second trap in yields ranging from 45 to 60%.

Propiolyl chloride is a clear, colorless liquid which fumes slightly in air and slowly turns yellow on standing at room temperature. It can be stored in the dark at Dry Ice temperature without appreciable decomposition.

Characterization. A. Spectroscopic Evidence. Ir spectra were recorded on a Beckman IR-20 grating spectrophotometer and the Raman spectrum on a Cary 81 He/Ne laser spectrophotometer. The pmr spectrum was obtained on a Perkin-Elmer R12A spectrometer with tetramethylsilane as the internal standard. The mass spectrum was run on a Hitachi Perkin-Elmer RMU-7 double-focusing instrument. The elemental analysis was carried out on a Perkin-Elmer Model 240 C, H, N analyzer.

The gas-phase infrared spectrum of propiolyl chloride shows the expected relatively simple spectrum. Five strong peaks are found above 300 cm^{-1}: 3332, 2120, 1771, 1000, and 659 cm^{-1}, which can readily be assigned to the HC≡, C≡C, C=O, C-C, and C-Cl stretching modes, respectively. The corresponding (liquid) Raman displacements are found at ~3300 (vw), 2118 (s), 1747 (ms), 1005 (w), and 653 cm^{-1} (s). The pmr spectrum in $CDCl_3$ shows one sharp singlet at τ 6.29.[4] The parent ion is very weak in the mass spectrum. The most prominent peaks occur for *m/e* 53.006 ($^{12}C_3{}^1H^{16}O$ = 53.003, 100%, $M^+ - Cl$). 59.979 ($^{12}C_2{}^1H^{35}Cl$ = 59.977, 15%, $M^+ - CO$), 28 (27%, CO), and 25 (25%, $M^+ - COCl$).

B. Chemical Evidence. 1. Propiolamide was prepared by reaction of a solution of propiolyl chloride in methylene chloride at −30° with ammonia. Insoluble ammonium chloride was removed by filtration and recrystallization of the propiolamide from chloroform gave white crystals: mp 58–58.5° (lit.[1] mp 60.5–61°); pmr ($CDCl_3$) τ 7.15 (s, 1, C≡CH) [lit.[5] pmr (CCl_4) τ 7.10]; mass spectrum (70 eV) *m/e* 69.021 ($^{12}C_3{}^1H_3{}^{14}N_1{}^{16}O$ = 69.022, 94%, M^+), 53 (100%, $M^+ - NH_2$), 44 (24%, $M^+ - C_2H$), 41 (52%, $M^+ - CO$).

2. 4.-Nitrophenyl propiolate was prepared by reaction of 4-nitrophenol with propiolyl chloride under similar conditions to those of Miller.[2c] Recrystallization from CCl_4 gave a white, crystalline solid, mp 135–135.5° (lit.[2c] mp 132–133°).

Anal. Calcd for $C_9H_5NO_4$: C, 56.54; H, 2.64; N, 7.33. Found (extended combustion): C, 55.93; H, 2.62; N, 7.23.

Ir ($CHCl_3$ solution) 3300 (≡CH), 3030 (ArH), 2130 (C≡C), 1755 (C=O), 1630, 1605, 1500 (aromatic C-C), 1540, 1360, (C-NO_2), 1185, 1020 cm^{-1} (ArO–); pmr ($CDCl_3$) τ 1.73 (m, 2) and 2.64 (m, 2) (ArH), 6.82 (s, 1, C≡CH); mass spectrum (70 eV) *m/e* 191.020 ($^{12}C_9{}^1H_5{}^{14}N^{16}O_4$ = 191.022, 9%, M^+), 174 (7%, M^+ − OH), 163 (11%, $M^+ - CO$), 53 (100%, $M^+ - C_6H_4NO_3$).

Acknowledgment. This research was supported by a grant from the National Research Council of Canada. The authors wish to thank Dr. D. Sutton of Simon Fraser University for assistance in recording the Raman spectrum of propiolyl chloride.

Registry No.—Propiolic acid, 471-25-0; phosphorus pentachloride, 10026-13-8; propiolyl chloride, 50277-65-1; 4-nitrophenyl propiolate, 35665-87-3.

References and Notes

(1) F. Straus and W. Voss, *Chem. Ber.*, **59**, 1681 (1926).
(2) (a) H. Riat and K. Seitz, German Patent 1,089,095 (1962); *Chem. Abstr.*, **56**, 4907*a* (1962); Swiss Patent 357,127 (1962); *Chem. Abstr.*, **56**, 15637*i* (1962). (b) F. C. Schaefer, U. S. Patent 2,388,660 (1946); *Chem. Abstr.*, **40**, 1868 (1946). (c) L. A. Miller, U. S. Patent 3,097,230 (1963); *Chem. Abstr.*, **59**, 13891*h* (1963).
(3) Monochloroacetylene is spontaneously inflammable in air: "Dictionary of Organic Compounds," 4th ed, I. Heilbron Ed., Eyre and Spottiswoode, London, i965, p 594.
(4) On prolonged standing, samples developed a weak AB quartet at τ 2.90 (Δ_{AB} = τ 1.20, J_{AB} = 13.6 Hz) in the pmr spectrum. These peaks can be assigned to *trans*-3-chloroacryloyl chloride, the product of the electrophilic addition of HCl to propiolyl chloride.
(5) (a) P. Jouve and M.-P. Simonnin, *C. R. Acad. Sci., Ser. C*, **257**, 121 (1963); (b) D. Rosenberg and W. Drenth, *Tetrahedron*, **27**, 3893 (1971).

Nuclear Magnetic Resonance and Stereochemical Assignments of a Double Diels–Alder Adduct.[1] A Demonstration of Steric Compression

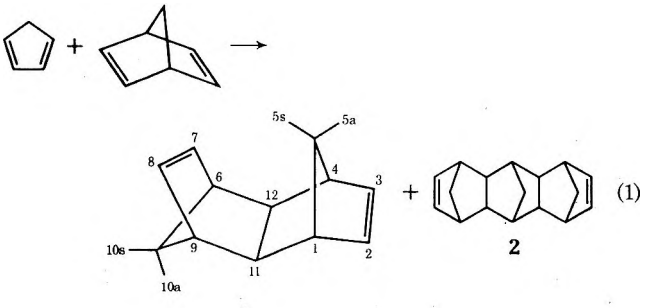
John Mantzaris and Edward Weissberger*

Department of Chemistry, Wesleyan University, Middletown, Connecticut 06457

Received August 10, 1973

During the course of our studies[2,3] of metal carbonyl induced coupling of olefins to carbon monoxide, we have considered the nmr and stereochemical assignments[3] of several polycyclic norbornyl systems. Difficulties encountered in assigning proton resonances only slightly downfield from an internal tetramethylsilane standard has caused us to consider the stereochemistry of a double Diels–Alder adduct.

Two products are obtained from the Diels–Alder reaction between cyclopentadiene and norbornadiene[4] (eq 1). Compound **2**, an adduct formed from two molecules of cyclopentadiene and one molecule of norbornadiene, is produced in addition to diene **1**. Marchand and Rose[5] first reported the nmr assignments of diene **1**. Their assignment was later elaborated upon by Wege,[6] who pointed out that the high-field doublet at δ 0.95 was due to the 5a proton. Proton 5s, which one might expect to be shielded by the Δ^7 bond, is in fact sterically deshielded.[6,7] By considering the stereochemistry of adduct **2**, we have confirmed this assignment. In Table I we report additional assignments for strained olefin **1**.



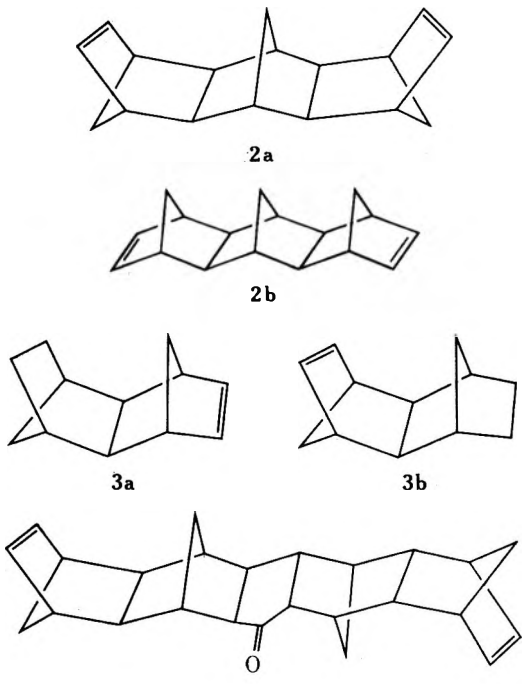
1 **2** (1)

The nmr spectra of **2** are shown in Figure 1 with assignments tabulated in Table II. Diene **2** shows but one olefinic resonance (δ 5.87), implying that **2** has a high degree of symmetry. Only two compounds, **2a** and **2b**, meet this requirement and have both external rings exo to the central ring. This latter requirement is discussed shortly.

The distinction between **2a** and **2b** is unequivocal and is based upon both spectral and reactivity data. First, the expected olefinic resonance for isomer **2b** is δ 6.17, corresponding to the appropriate resonance found for diene **1** and the corresponding monoene,[2] **3a**. The observed olefinic resonance at δ 5.87 corresponds to the 7,8 protons of **1** and the observed resonance for the monoene[2] **3b**.

Table I
Chemical Shift and Coupling Constant Assignments for Diene 1

Proton	Chemical shift, δ ppm	Coupling constant	Hz
1, 4	2.47	$J_{1,5s}$	1.8
2, 3	6.17	$J_{1,5a}$	1.1
5a	0.95	$J_{1,2}$	1.6
5s	2.60	$J_{5a,5s}$	8.5
6, 9	2.64	$J_{5a,11}$	0.6
7, 8	5.99	$J_{5s,2}$	0.3
10a	1.19	$J_{6,7}$	2.0
10s	1.33	$J_{6,10}$	1.7
11, 12	2.19	$J_{6,12}$	0.8
		$J_{7,10a}$	0.5
		$J_{10a,10s}$	7.7



Of equal importance is the reactivity of 2 toward coupling by $Fe(CO)_5$. When diene **1** is treated with $Fe(CO)_5$, it couples[2,3] to form ketone **1a**. Monoene **3a** is also reactive in that it couples to the corresponding ketone, while **3b** is unreactive. On the basis of these data, we would expect **2a** to be unreactive while **2b** would easily couple to a series of ketonic products. Diels–Alder adduct **2** is unreactive, leading us to conclude that **2a** depicts the correct stereochemistry of the double Diels–Alder adduct.

Spin-decoupling studies have been particularly helpful in analyzing the nmr spectrum of **2a**. Irradiation at δ 2.80 (6, 9 protons decoupled) markedly changes the spectrum. The triplet at δ 5.87 collapses to a sharp singlet ($J_{6,7}$ = 2.0 Hz) while the triplet assigned to the 2,3 protons at δ 1.82 reduces to a moderately sharp singlet ($J_{3,6}$ = 2.0 Hz). Further, the AB pattern of the doublet of triplets assigned to the 10s,10a protons centered at δ 1.23 is converted to a simple AB pattern of singlets with a 10a,10s geminal coupling constant of 8.0 Hz. The poorly resolved triplet centered at δ 1.92, assigned to the bridgehead (1,4) protons, sharpens to a well-resolved triplet (J = 2.0 Hz). This sharpening is due to the removal of long-range coupling ("W" rule) between protons 1 and 9. The triplet could be due to proton 1 coupled to the two equivalent number 2 protons, or to the equivalent (5) bridge protons. Decoupling the 2,3 protons at δ 1.82 does not change the 1,4 triplet, suggesting that the 1,4 protons are coupled to the bridge (5) protons. This is not unusual for coupling between bridge and bridgehead protons in norbornyl systems.[8] Further, the fact that $J_{1,2}$ is unobserved implies[9] that the 2,3 protons are endo to the central norbornyl ring. Long-range coupling between protons 2,3 with 5′ is observed when the 2,3 protons are irradiated.

Table II
Chemical Shift and Coupling Constant Assignments for Olefin 2

Proton	Chemical shift, δ ppm	Coupling constant	Hz
1, 4	1.92	$J_{1,5}$	2.0
2, 3	1.82	$J_{2,8}$	1.0
5, 5′	1.53	$J_{3,6}$	2.0
6, 9	2.80	$J_{6,7}$	2.0
7, 8	5.87	$J_{9,10}$	1.5
10a	1.17	$J_{10a,10s}$	8.0
10s	1.28		

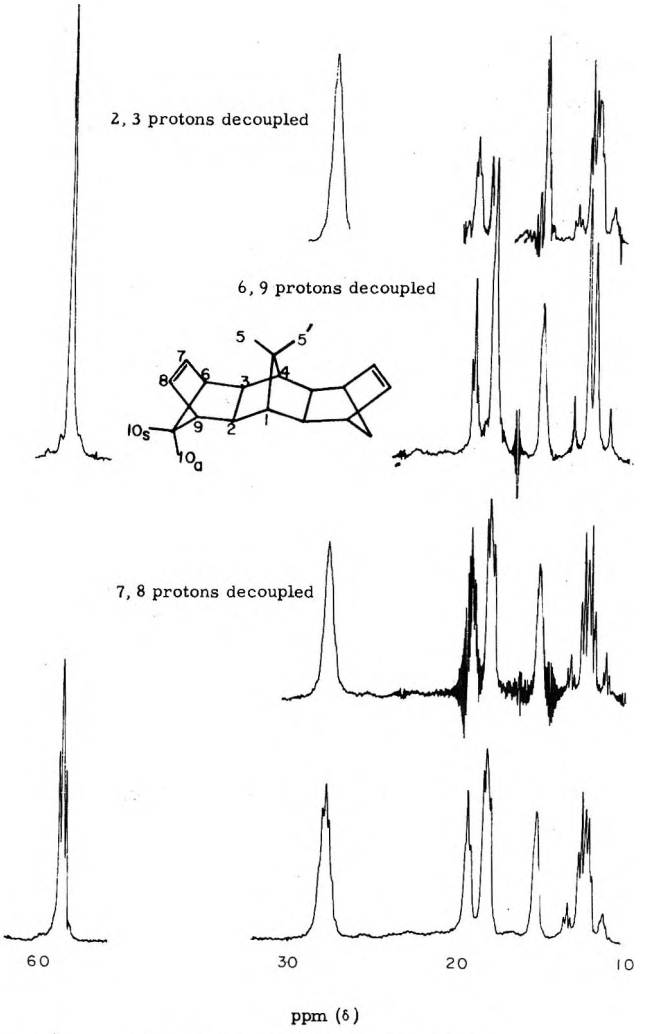


Figure 1. 90-MHz spectrum of Diels–Alder adduct **2**.

Additional decoupling studies provide data which allow chemical shifts to be assigned to the 10s and 10a protons. Irradiation at δ 5.87 decouples the olefinic protons and sharpens the high-field portion of the AB pattern corresponding to the 10s,10a protons. This is due to the loss of stereospecific coupling between the 7(8) and 10a protons. Therefore, the high-field absorption centered at δ 1.17 is assigned to proton 10a while the absorption centered at δ 1.28 is assigned to the 10s proton. Similar conclusions are reported in the literature.[5,10] The triplet assigned to the 2,3 protons also sharpens, since long-range coupling between protons 2 and 8 is removed.

In view of the assignment of 2 to stereochemistry **2a** and the observation that the bridge protons (5) absorb at δ 1.53, there being no high-field resonance, we conclude that steric deshielding of the 5s protons in compounds such as 1 is operative.

Experimental Section

Proton magnetic resonance spectra were obtained in $CDCl_3$ on a Bruker 90-MHz spectrometer and are reported downfield from an internal tetramethylsilane (TMS) standard. Diels–Alder adducts were prepared according to literature procedures.[4] We did find that the Diels–Alder reaction could be efficiently carried out in an annealed glass pressure bottle (Fisher and Porter) fitted with a pressure gauge, gas inlet, and pressure-release valve. Standard chromatographic and liquid–liquid extraction procedures were applied where appropriate.

Acknowledgment. Financial support from Wesleyan University and a fellowship to one of us (J. M.) are gratefully acknowledged. We especially wish to thank Dr. T. H. Regan of the Eastman Kodak Co. for obtaining the 90-MHz spectra for us.

Registry No.—**1**, 15914-94-0; **2a**, 50415-43-5.

References and Notes

(1) Taken in part from the Ph.D. Thesis of J. Mantzaris, Wesleyan University, 1973.
(2) J. Mantzaris and E. Weissberger, *Tetrahedron Lett.*, 2815 (1972).
(3) J. Mantzaris and E. Weissberger, *J. Amer. Chem. Soc.*, in press.
(4) (a) J. K. Stille and D. A. Frey, *J. Amer. Chem. Soc.*, **81**, 4273 (1959); (b) J. K. Stille and D. R. Witherell, *ibid.*, **86**, 2188 (1964).
(5) A. P. Marchand and J. E. Rose, *J. Amer. Chem. Soc.*, **90**, 3724 (1968).
(6) R. McCulloch, A. R. Rye, and D. Wege, *Tetrahedron Lett.*, 5163 (1969).
(7) S. Winstein, P. Carter, F. A. L. Anet, and A. J. R. Bourn, *J. Amer. Chem. Soc.*, **87**, 5249 (1965).
(8) E. I. Synder and B. Franzus, *J. Amer. Chem. Soc.*, **86**, 1166 (1964).
(9) M. Karplus, *J. Amer. Chem. Soc.*, **85**, 2870 (1963).
(10) B. Franzus, W. C. Baird, Jr., N. F. Chamberlain, T. Hines, and E. I. Snyder, *J. Amer. Chem. Soc.*, **90**, 3721 (1968).

Nucleophilic Reactions of α-Bromoacetophenone Oxime. Preparation of *anti*-Acetophenone Oxime

Jerry H. Smith

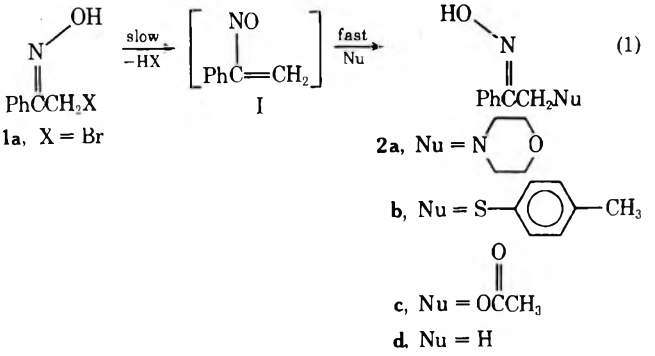
Department of Chemistry, Marquette University, Milwaukee, Wisconsin 53233

E. T. Kaiser*

Searle Chemistry Laboratory, University of Chicago, Chicago, Illinois 60637

Received October 15, 1973

We have recently described the reaction of α-halo oximes with nucleophiles which involves the stereoselective trapping of a reactive intermediate.[1] This reaction can be summarized by eq 1, where X is halogen and Nu is a nucleophile. As shown, it was suggested that the intermediate might be α-nitrosostyrene (I), which reacts more rapidly in the s-trans conformation than in the s-cis, giving the thermally unstable anti alkyl aryl ketoxime isomer.[2] The preparation of the previously unknown *anti*-α-bromoacetophenone oxime from **2a** which had been obtained by the route of eq 1 was also reported.[1b] To explore the general synthetic utility of this reaction and to gain further insight into its mechanism, we have varied the nature of the nucleophile Nu in eq 1. In the present communication we report the results of this investigation, including the facile, one-step conversion of **1a** to *anti*-acetophenone oxime (**2d**), a previously unisolated material.



When **1a** dissolved in acetonitrile is added to an aqueous acetonitrile solution of $NaBH_4$, rapid evolution of a gas takes place. After 5 min at room temperature, extraction of the reaction mixture gives in high yield *anti*-acetophenone oxime (**2d**). In the nmr spectrum ($CDCl_3$), absorption due to the methyl group of **2d** occurs at δ 2.20 ppm while the corresponding resonance in the syn isomer is detected at 2.28 ppm.[3] The uv spectrum for **2d** in ethanol has λ_{max} 235 nm (log ϵ 3.86) compared to λ_{max} 245 nm (log ϵ 4.10) for the syn isomer. This difference is in agreement with previously reported spectra for isomeric alkyl aryl oximes.[1a,4] When **2d** was refluxed in chlorobenzene solution, there was a gradual decrease in intensity of the methyl resonance at 2.20 ppm and a corresponding increase in intensity of a peak at 2.28 ppm, resulting in a final mixture composed of 5% **2d** and 95% of the thermally generated product. This material was isolated and identified as *syn*-acetophenone oxime. A sample of **2d** was subjected to Beckmann rearrangement conditions and the major product obtained was *N*-methylbenzamide, confirming the stereochemical assignment.[5]

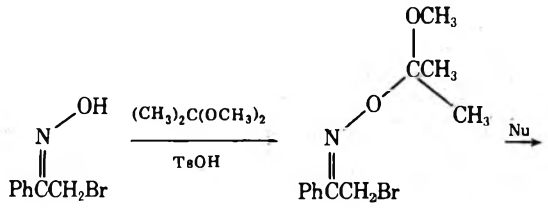
The borohydride reduction of **1a** to give **2d** takes place in ethanol and 1,2-dimethoxyethane as well as in aqueous acetonitrile. In each of these solvents, 1 mol of $NaBH_4$ is required for each mole of **1a** reduced. When 0.5 mol of $NaBH_4$ is used, 50% of **1a** is converted to **2d** while the remaining 50% is recovered. The reaction was complete within 5 min at room temperature and longer reaction times did not affect the yields or isomeric composition of the product. In a control experiment, *syn*-acetophenone oxime was recovered unreacted from an aqueous acetonitrile solution of $NaBH_4$. This finding agrees with results of previous workers.[6]

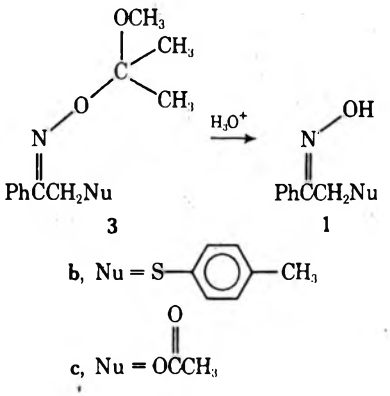
The conversion of **1a** to **2d** is thought to proceed *via* intermediate I of eq 1. The HBr produced would be expected to react with $NaBH_4$ to release hydrogen gas. If intermediate I is in fact α-nitrosostyrene, as has been proposed,[1b] then the postulated $NaBH_4$ reduction of I would be reasonable. It is known that the carbon–carbon double bond of 1-nitro alkenes[7] and α,β-unsaturated aldehydes and ketones[8] can be reduced by $NaBH_4$ to give the corresponding 1-nitro alkanes and saturated alcohols. Conjugate addition of borohydride to the proposed α-nitrosostyrene would result in an oxime product which is inert to further reduction. The anti stereochemistry of the product is in agreement with the previous results obtained with displacement by morpholine.[1]

We have also investigated the reaction of **1a** with sulfur and oxygen nucleophiles. When *p*-tolyl thiolate is added to **1a** in aqueous solution, the product isolated is *anti*-α-(*p*-tolylthio)acetophenone oxime (**2b**). The nmr spectrum ($CDCl_3$) of **2b** is similar to that of the syn isomer **1b**, prepared by an independent route (eq 2), except that the methylene resonance is shifted upfield by 0.27 ppm (δ 4.17 for the syn isomer and δ 3.90 for the anti isomer).[3] Thermal isomerization of **2b** in $CDCl_3$ resulted in a mixture of

14% **2b** and 86% of the thermally generated product identified as **1b**.

When **1a** was allowed to react with aqueous sodium acetate, *anti*-α-acetoxyacetophenone oxime (**2c**) was isolated. The nmr spectrum ($CDCl_3$) of **2c** showed a two-proton singlet at δ 4.97 and a three-proton singlet at δ 1.95. The corresponding peaks for the syn isomer **1c** (prepared as in eq 2) are δ 5.30 and 2.00.[3] Thermal isomerization of **2c** in





(2)

a manner analogous to that of **2b** resulted in a mixture containing 20% **2c** and 80% of the thermally generated product identified as **1c**.[9]

From the above results, it appears that the preparation of α-substituted oximes from the corresponding α-bromo oxime can be readily achieved with oxygen, nitrogen, and sulfur nucleophiles. The anti isomers can be produced directly from the *syn*-α-bromo oxime (eq 1) while the syn isomers can be prepared by first protecting the oxime function (eq 2). The sodium borohydride reduction of α-halo oximes may prove to be a generally useful synthetic route to thermally unstable anti alkyl aryl ketoximes.

Experimental Section

All melting points are uncorrected. Nmr spectra were obtained on Varian A-60 or A-60A spectrometers. Uv spectra were obtained on a Cary 15 instrument.

***anti*-Acetophenone Oxime (2d).** A 1.0-g (4.7 mmol) portion of **1a** dissolved in 10 ml of CH_3CN was added to a stirred solution of 177 mg (4.7 mmol) of $NaBH_4$ in 60 ml of water and 20 ml of CH_3CN at room temperature. Rapid evolution of a gas occurred but ceased within a few minutes. The pH dropped from 8 to 6 during this period. After 5 min the reaction mixture was extracted with $CHCl_3$ to give 624 mg of white solid which contained 90% *anti*- and 10% *syn*-acetophenone oxime as measured by nmr. This material was crystallized from $CHCl_3$–petroleum ether (bp 30–60°): mp 81–83°; nmr ($CDCl_3$) δ 9.7 (1 H, broad), 7.3–7.7 (5 H, m), 2.20 (3 H, s); uv λ_{max} (EtOH) 235 nm (log ε 3.86), λ_{max} (hexane) 231 nm (log ε 3.89).

Anal. Calcd for C_8H_9NO: C, 71.09; H, 6.71; N, 10.36. Found: C, 70.89; H, 6.72; N, 10.30.

Thermal Isomerization of 2d. A 500-mg portion of **2d** was dissolved in chlorobenzene and refluxed at 132°. An nmr analysis showed that the equilibrium mixture consisted of 5% **2d** and 95% *syn*-acetophenone oxime. This material was crystallized from petroleum ether, mp 58.5–59.5°, mmp with *syn*-acetophenone oxime 59.5–60.5°.

Beckmann Rearrangement of 2d. To a stirred suspension of 242 mg (1.16 mmol) of PCl_5 in 5 ml of benzene was added 157 mg (1.16 mmol) of 2d dissolved in 5 ml of benzene. After 1.0 hr at room temperature, the reaction mixture was combined with 10 ml of benzene in a separatory funnel. Water was added and the mixture was shaken well. After extractions with 10% K_2CO_3 and water, the benzene portion gave 82 mg of white solid. A $CHCl_3$ extraction of the aqueous portion gave an additional 63 mg of white solid. An nmr analysis indicated that 80% of the recovered 145 mg of material was *N*-methylbenzamide. The remaining 20% was acetanilide.

Borohydride Reduction of 1a in Ethanol and Dimethoxyethane (DME). The procedure followed here was similar to that for the aqueous CH_3CN reaction described above except that ethanol or DME were used as solvents. With DME the reaction mixture was heterogeneous owing to the low solubility of $NaBH_4$ in that solvent. The work-up for both solvents consisted of adding the reaction mixture to water and extracting with $CHCl_3$. The major product obtained in each solvent was identified by nmr as *anti*-acetophenone oxime.

Stoichiometry of the Borohydride Reduction of 1a. The reductions described above for aqueous CH_3CN, EtOH, and DME solvents were carried out on a small scale with accurately weighed reagents. The borohydride was assayed by an iodometric procedure[10] and found to be approximately 100% pure. An aqueous solution of $NaBH_4$ at pH 8 showed no deterioration after 5 min at room temperature. The ratio of materials obtained by extraction of the reaction mixtures was determined by nmr. When 1.0 mol of $NaBH_4$ was used, the yield of acetophenone oxime was greater than 97%. When 0.5 mol of $NaBH_4$ was used, the yield ranged from 41 to 52%. These yields are based on the recovered mixture of starting material **1a** and products, which was typically about 95% of the theoretical amount.

Control Reaction of $NaBH_4$ with *syn*-Acetophenone Oxime. A 190-mg (1.4 mmol) portion of *syn*-acetophenone oxime in 3 ml of CH_3CN was added to 53 mg (1.4 mmol) of $NaBH_4$ dissolved in a mixture of 20 ml of water and 7 ml of CH_3CN. After 30 min at room temperature, $CHCl_3$ extraction gave 183 mg of material identified by nmr as recovered *syn*-acetophenone oxime.

***anti*-α-(*p*-Tolylthio)acetophenone Oxime (2b).** The solvents used in the preparation of **2b** were deoxygenated by bringing to reflux and cooling under a stream of nitrogen. A solution of *p*-tolyl thiolate was prepared by adding 100 ml of an ethanolic solution containing 6.2 g (0.05 mol) of *p*-toluenethiol to a solution containing 0.05 mol of NaOH in 300 ml of water and 50 ml of ethanol. This slightly turbid solution was stirred under a stream of nitrogen while 2.14 g (0.01 mol) of *syn*-α-bromoacetophenone oxime (**1a**) in 50 ml of ethanol was added. After a few minutes at room temperature, the resulting solution (very turbid) was extracted with $CHCl_3$ to give 2.4 g of an oil which solidified when the last traces of solvent were removed. Crystallization from CCl_4–petroleum ether gave colorless needles: mp 84.0–85.0°; nmr ($CDCl_3$) δ 8.5 (1 H, broad), 7.0–7.5 (9 H, m), 3.90 (2 H, s), 2.28 (3 H, s).

Anal. Calcd for $C_{15}H_{15}NOS$: C, 69.99; H, 5.88; N, 5.45; S, 12.47. Found: C, 70.04; H, 5.92; N, 5.42; S, 12.35.

Thermal Isomerization of 2b. A 100-mg portion of **2b** was dissolved in $CDCl_3$, placed in a sealed nmr tube, and heated at 100° until nmr analysis showed no further change. The equilibrium mixture consisted of 14% **2b** and 86% **1b**. The mixture was crystallized from hexane, mp 83.5–84.0°, mmp with **1b** 83.5–84.5°.

***anti*-α-Acetoxyacetophenone Oxime (2c).** To a stirred solution of 14 g (0.1 mol) of sodium acetate trihydrate in 200 ml of water and 50 ml of CH_3CN was added 2 g (0.009 mol) of **1a** in 40 ml of CH_3CN. After 1 hr at room temperature, the reaction mixture was extracted with $CHCl_3$ to give 1.7 g of an oil which was crystallized from $CHCl_3$–petroleum ether: mp 47.5–49.5°; nmr ($CDCl_3$) δ 8.4 (1 H, broad), 7.3–7.7 (5 H, m), 4.97 (2 H, s), 1.95 (3 H, s).

Anal. Calcd for $C_{10}H_{11}NO_3$: C, 62.17; H, 5.74; N, 7.25. Found: C, 61.97; H, 5.78; N, 7.21.

Thermal Isomerization of 2c. A 63-mg portion of **2c** was subjected to conditions similar to **2b** described above. The equilibrium mixture contained 20% **2c** and 80% **1c**. The isomerization product could not be crystallized but had an nmr spectrum identical with that of **1c**.

***syn*-α-Bromoacetophenone Oxime Ketal (3a).** A solution of 1.0 g (4.68 mmol) of **1a**, 2.44 g (23.4 mmol) of 2,2-dimethoxypropane, 45 mg (0.23 mmol) of *p*-toluenesulfonic acid monohydrate, and 20 ml of CH_2Cl_2 was refluxed overnight. The solution was extracted with 1 *M* $NaHCO_3$ and the solvent was removed to give 1.22 g of an oil, nmr ($CDCl_3$) δ 7.3–7.85 (5 H, m), 4.37 (2 H, s), 3.33 (3 H, s), 1.57 (6 H, s).

***syn*-α-(*p*-Tolylthio)acetophenone Oxime Ketal (3b).** *p*-Toluenethiol (0.54 g, 4.34 mmol) was dissolved in 50 ml of deoxygen-

ated EtOH, and 2.0 ml of an aqueous 2.08 *M* NaOH solution was added. To this slightly turbid solution was added 0.62 g (2.17 mmol) of **3a** in 5 ml of EtOH. The reaction mixture was stirred at room temperature overnight. The solvent was evaporated and the residue was dissolved in ether and extracted with 10% K_2CO_3 solution. Removal of the ether gave 0.61 g of an oil, nmr ($CDCl_3$) δ 7.0–7.7 (9 H, m), 4.12 (2 H, s), 3.20 (3 H, s), 2.30 (3 H, s), 1.42 (6 H, s).

syn-α-(*p*-**Tolylthio)acetophenone Oxime (1b).** A solution of 0.61 g of **3b** in 10 ml of CH_3CN was added to a mixture of 100 ml of aqueous 0.1 *M* HCl and 40 ml of CH_3CN and was stirred at room temperature for 30 min. Extraction of the heterogeneous reaction mixture with $CHCl_3$ gave 0.49 g of an oil which was crystallized from hexane: mp 84.0–85.0°; mmp with **2b** 61.5–66.0°; nmr ($CDCl_3$) δ 8.9 (1 H, broad), 6.9–7.65 (9 H, m), 4.17 (2 H, s), 2.28 (3 H, s).

Anal. Calcd for $C_{15}H_{15}NOS$: C, 69.99; H, 5.88; N, 5.45; S, 12.47. Found: C, 70.08; H, 5.88; N, 5.47; S, 12.47.

syn-α-**Acetoxyacetophenone Oxime Ketal (3c).** A heterogeneous mixture containing 0.6 g (2.1 mmol) of **3a**, 1.0 g (7.35 mmol) of sodium acetate trihydrate, and 70 ml of CH_3CN was refluxed overnight. The reaction mixture was cooled and filtered, and the solvent was removed from the filtrate. The residue was taken up in ether and extracted with bicarbonate solution. The ether was removed to give 0.51 g of an oil, nmr ($CDCl_3$) δ 7.3–7.75 (5 H, m), 5.26 (2 H, s), 3.28 (3 H, s), 1.97 (3 H, s), 1.53 (6 H, s).

syn-α-**Acetoxyacetophenone Oxime (1c).** Removal of the ketal group was similar to the procedure for **1b**. Work-up gave 380 mg of an oil which could not be crystallized, nmr ($CDCl_3$) δ 9.8 (1 H, broad), 7.2–7.7 (5 H, m), 5.30 (2 H, s), 2.00 (3 H, s).

Acknowledgment. The support of this research by a grant from the donors of the Petroleum Research Fund, administered by the American Chemical Society (E. T. K.), and an Alfred P. Sloan Foundation Fellowship (E. T. K.) is gratefully acknowledged.

Registry No.—1a, 17082-13-2; **1b,** 50314-81-3; **1c,** 50314-82-4; **1d,** 10341-75-0; **2b,** 50314-84-6; **2c,** 50314-85-7; **2d,** 50314-86-8; **3a,** 50314-87-9; **3b,** 50314-88-0; **3c,** 50314-89-1.

References and Notes

(1) (a) J. H. Smith, J. H. Heidema, E. T. Kaiser, J. B. Wetherington, and J. W. Moncrief, *J. Amer. Chem. Soc.*, **94**, 9274 (1972); (b) J. H. Smith, J. H. Heidema, and E. T. Kaiser, *ibid.*, **94**, 9276 (1972).
(2) Throughout this article, syn refers to the isomer having the alkyl group cis to the oxime oxygen; anti refers to the isomer having the alkyl group trans to the oxime oxygen.
(3) This is in general agreement with previous findings that resonances due to the protons of alkyl and aldehyde groups trans to the oxime oxygen appear upfield from the corresponding protons in the syn isomer. See, for example, G. J. Karabatsos, R. A. Taller, and F. M. Vane, *J. Amer. Chem. Soc.*, **85**, 2326, 2327 (1963); I. Pejkovic-Tadic, M. Hranisavljevic-Jakovljevic, S. Nesic, C. Pascual, and W. Simon, *Helv. Chim. Acta*, **48**, 1157 (1965).
(4) H. P. Fischer and C. A. Grob, *Helv. Chim. Acta*, **45**, 2528 (1962).
(5) L. G. Donaruma and W. Z. Heldt, *Org. React.*, **11**, 1 (1960).
(6) K. H. Bell, *Aust. J. Chem.*, **23**, 1415 (1970).
(7) A. I. Meyers and J. C. Sircar, *J. Org. Chem.*, **32**, 4134 (1967).
(8) M. R. Johnson and B. Rickborn, *J. Org. Chem.*, **35**, 1041 (1970).
(9) For identification of the products from the thermally induced reactions described above, samples of the syn isomers **1b** and **1c** were prepared by the route of eq 2. Protection of the oxime function prevents formation of intermediate I (eq 1) and direct displacement of bromide by nucleophile Nu occurs. The conditions for removal of the ketal group do not cause isomerization of the oxime function.[1a] This route is more lengthy than direct reaction of the appropriate ketone with hydroxylamine or its salts. However, it allows the preparation of oximes containing functionalities that would be reactive toward hydroxylamine, such as the acetoxy group.
(10) P. K. Norkus, *J. Anal. Chem. USSR*, **24**, 1369 (1969).

Communications

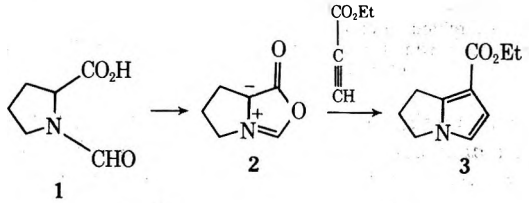
Stereospecific Synthesis of 1-Substituted Pyrrolizidines[1]

Summary: A two-step stereospecific route to 1-substituted pyrrolizidines was achieved from *N*-formyl-L-proline.

Sir: Interest in the 1-substituted pyrrolizidine skeleton derives chiefly from its presence in a number of widely distributed alkaloids[2] and from the pharmacological activity of these compounds.[3]

Previous syntheses of 1-substituted pyrrolizidines are multiple-step procedures.[4] This report describes a two-step stereospecific route that gives the thermodynamically less stable racemate **5** in 80% overall yield. Since complete epimerization at C_1 to the more stable racemate is known to proceed with high yield,[5] this is a preparative procedure to obtain derivatives of the heliotridane **4** and pseudoheliotridane **7** series, from a single intermediate **3**.

The synthesis was accomplished starting with the readily available *N*-formyl-L-proline[6] (**1**) [mp 88–91°, $[\alpha]^{20}D$ −125° (c 1, EtOH)] prepared in quantitative yield from L-proline and acetic–formic anhydride. Cycloaddition of ethyl propiolate to **1** (5 equiv of ethyl propiolate in acetic anhydride at reflux for 2 hr) afforded the ester **3**[6] in 90% yield after silica gel column chromatography using chloroform as eluent.



1 **2** **3**

4, R = CH_3
5, R = CO_2Et
6, R = CH_2OH

7, R = CH_3
8, R = CO_2Et
9, R = CH_2OH

It is reasonable to assume that a 1,3 dipole,[7] **2**, is the intermediate in the conversion of **1** to **3**.

Hydrogenation of **3** was carried out in ethanol as solvent under 3 atm of hydrogen for 24 hr with 10% palladium on carbon (amount equal weight of substrate **3**) to afford the stereochemically pure[8] ethyl (±)-isoretronecanolate (**5**)[6] in 93% yield, picrate mp 119–121° (lit.[4b] mp 119.5–120°), picrolonate mp 183–189° (lit.[4b] mp 186–189°). Reduction of **5** to (±)-isoretronecanol (**6**), picrate mp 187–189° (lit.[4b] 189.5–190°), picrolonate mp 174–176° (lit.[4b] 176–177°), as described[4b] provided final identification of the structure and stereochemistry of product **5**.

References and Notes

(1) This investigation was supported by grants from the National Research Council (Argentina).
(2) N. J. Leonard, in "The Alkaloids," R. H. Manske, Ed., Vol. VI, Academic Press, New York, N. Y., 1959, p 35.
(3) A. R. Pomeroy and C. Raper, *Eur. J. Pharmacol.*, **14**, 374 (1971), and references cited therein.
(4) (a) N. D. Nair and R. Adams, *J. Org. Chem.*, **26**, 3059 (1961); (b) N. J. Leonard and T. Sato, *J. Org. Chem.*, **34**, 1066 (1969), and references cited therein.
(5) A. M. Likhosherstov, V. N. Kulkov, and N. K. Kochetkov, *Zh. Obshch. Khim.*, **34**, 2798 (1964).
(6) Satisfactory ir and nmr spectra and C, H, and N analytical data have been obtained for this substance.
(7) H. O. Bayer, H. Gotthardt, and R. Huisgen, *Chem. Ber.*, **103**, 2356 (1970).
(8) Thin layer chromatography is the best procedure for detection of impurities in this type of compounds; see A. H. Chalmers, C. C. J. Culvenor, and W. Smith, *J. Chromatogr.*, **20**, 270 (1965).

Facultad de Farmacia y Bioquimica
Junin 956,
Buenos Aires, Argentina

Maria T. Pizzorno
Sem M. Albonico*

Received November 30, 1973

The Convenient Stereospecific Synthesis of Terminal Acetylenes *via* the Treatment of Lithium Ethynyltrialkylborates with Iodine

Summary: Lithium ethynyltrialkylborates, readily prepared from lithium acetylide–ethylenediamine and trialkylboranes, react readily with iodine to produce in high yield the corresponding terminal alkylacetylene with complete retention of the stereochemistry of the boron–carbon bond.

Sir: Treatment of lithium 1-alkynyltrialkylborates with iodine under very mild conditions produces the corresponding internal acetylenes in essentially quantitative yields[1] (eq 1). However, when we attempted to extend

$$Li[R_3BC{\equiv}CR'] + I_2 \longrightarrow RC{\equiv}CR' \qquad (1)$$

this synthesis to the preparation of the corresponding terminal acetylenes, the results were highly unsatisfactory. For example, treatment of monolithium acetylide[2] with tri-*n*-butylborane produced the lithium ethynyltri-*n*-butylborate (^{11}B nmr +17.3 ppm). Treatment of this complex with iodine at −78° provided 1-hexyne in a yield of only 24% (glpc analysis). However, when the commercially available lithium acetylide–ethylenediamine[3] was used, the reaction proved far more favorable. Addition of 1 molar equiv of tri-*n*-butylborane to a suspension of the reagent in tetrahydrofuran (THF) resulted in a slightly exothermic reaction and solution of the suspension. Addition of iodine at −78° followed by warming to room temperature produced 1-hexyne in a yield of 75%.

The reaction was then applied to representative organoboranes. Even better results, in the range of 84–94%, were obtained with the great majority of the trialkylboranes.[4] Representative results are summarized in Table I.

The following procedure for the preparation of cyclohexylethyne is representative. A dry 100-ml flask equipped with septum inlet and magnetic stirring bar was flushed with nitrogen. The flask was charged with 2.02 ml of 2.46 *M* borane in THF (5.0 mmol of borane) and 7 ml of dry THF. Cyclohexene (15.0 mmol) was added to the solution and the mixture stirred overnight at room temperature. (Alternatively, the solution may be heated at 50° for 3 hr to complete the hydroboration of this relatively sluggish olefin.) To the solution was added 0.50 g (5.09 mmol) of lithium acetylide–ethylenediamine (Ventron Corp.). (The lithium acetylide reacts slowly with air and moisture and should be handled in a glove bag.) The solution was

Table I
Synthesis of Terminal Acetylenes by the Treatment of Lithium Ethynyltrialkylborates–Ethylenediamine with Iodine

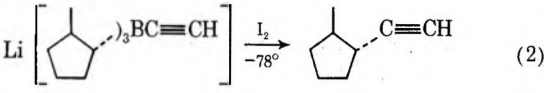
Olefin in R_3B	Product	Yield, %[a]
1-Butene	1-Hexyne	75
2-Butene	3-Methyl-1-pentyne	84
2-Methylpropene	4-Methyl-1-pentyne	94
Cyclopentene	Cyclopentylethyne	85
1-Methylcyclopentene	*trans*-2-Methylcyclopentylethyne	90
Cyclohexene	Cyclohexylethyne	92

[a] Analysis by glpc with yield based on R_3B.

stirred for 2 hr at room temperature and then cooled to −78°. Iodine, 1.27 g (5.0 mmol), in 6 ml of THF was added dropwise to the solution with vigorous stirring. After 90 min at −78°, the solution was brought to room temperature and treated with 5 ml of 40% potassium hydroxide, and the aqueous phase saturated with potassium carbonate. Analysis by glpc revealed the presence of 4.6 mmol (92% yield) of cyclohexylethyne.

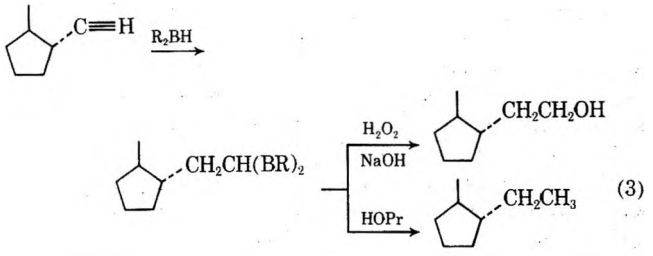
Many reactions of organoboranes proceed to provide products which retain the stereochemistry of the boron–carbon bond.[5] On the other hand, some reactions which proceed through free-radical intermediates involve the loss of such stereochemistry.[6] Accordingly, it appeared desirable to establish the stereochemistry of the present synthesis.

The trialkylborane from 1-methylcyclopentene was selected for this study. Oxidation with alkaline hydrogen peroxide produces 100% *trans*-2-methylcyclopentanol, with only a trace of 1-methylcyclopentanol.[5] The acetylene product obtained from this organoborane was indicated to be a single isomer, presumably the trans derivative (eq 2) by glpc analysis.



(2)

This conclusion was confirmed by dihydroborating the product with dicyclohexylborane (R_2BH). Oxidation with alkaline hydrogen peroxide[7] produced 2-(*trans*-2-methylcyclopentane)ethanol and protonolysis[8] with propionic acid produced *trans*-1-ethyl-2-methylcyclopentane (eq 3). In each case, the isomeric purity of the products was confirmed by glpc comparison with authentic samples of the *cis* and *trans* isomers. In both cases, only the trans isomers could be detected.



(3)

One of the major conventional methods for the preparation of terminal acetylenes involves nucleophilic displacement of halides or sulfates by the acetylide ion. The reaction proceeds in a satisfactory manner only with those primary derivatives which readily participate in S_N2 substitution processes. However, the present procedure accommodates, in addition to primary alkyl groups, highly branched groups, secondary, and alicyclic groups, groups which are often relatively resistant to nucleophilic substitution. Furthermore, the transfer of alkyl groups from boron to the acetylenic carbon with retention further extends the range of applicability of this procedure. Consequently, this development provides a general, stereospecific synthesis of monoalkyl- and monocycloalkylacetylenes under exceptionally mild conditions. The discovery that lithium acetylide–ethylenediamine may be used to prepare lithium ethynyltrialkylborates now makes possible the extension of the many interesting new reactions of the lithium 1-alkynyltriorganoborates[9] to the parent compound.

References and Notes

(1) A. Suzuki, N. Miyaura, S. Abiko, M. Itoh, H. C. Brown, J. A. Sinclair, and M. M. Midland, *J. Amer. Chem. Soc.*, **95**, 3080 (1973).
(2) The lithium acetylide was prepared by the addition of *n*-butyllithium to acetylene in THF at −78°. Addition of acetone yielded 94% 2-methyl-3-butyn-2-ol, confirming that the lithium acetylide had been formed in high yield. Following an alternative literature procedure [K. Suga, S. Watanabe, and T. Suzuki, *Can. J. Chem.*, **46**, 3041 (1968)] for the preparation of lithium acetylide resulted in a yield of 1-hexyne of only 6%.
(3) O. F. Beumel, Jr., and R. F. Harris, *J. Org. Chem.*, **28**, 2775 (1963).
(4) Triphenylborane failed to give phenylethyne under these conditions.
(5) H. C. Brown, "Boranes in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1972.
(6) H. C. Brown, M. M. Midland, and G. W. Kabalka, *J. Amer. Chem. Soc.*, **93**, 1024 (1971).
(7) G. Zweifel and H. Arzoumanian, *J. Amer. Chem. Soc.*, **89**, 291 (1967).
(8) H. C. Brown and K. Murray, *J. Amer. Chem. Soc.*, **81**, 4108 (1959).
(9) P. Binger, G. Benedikt, G. W. Rotermund, and R. Köster, *Justus Liebigs Ann. Chem.*, **717**, 21 (1968); P. Binger and R. Köster, *Tetrahedron Lett.*, 1901 (1965); P. Binger and R. Köster, *Synthesis*, 309 (1973); M. Naruse, T. Tomita, K. Utimoto, and H. Nozaki, *Tetrahedron Lett.*, 795 (1973); M. Naruse, K. Utimoto, and H. Nozaki, *ibid.*, 1847, 2741 (1973); A. Pelter, C. R. Harrison, and D. Kirkpatrick, *J. Chem. Soc. D*, 544 (1973); A. Pelter, C. R. Harrison, and D. Kirkpatrick, *ibid.*, in press; E. Negishi, G. Lew, and T. Yoshida, *ibid.*, submitted for publication.
(10) Graduate research assistant on Grant No. GM 10937 from the National Institutes of Health.

Richard B. Wetherill Laboratory
Purdue University
West Lafayette, Indiana 47907

M. Mark Midland
James A. Sinclair[10]
Herbert C. Brown*

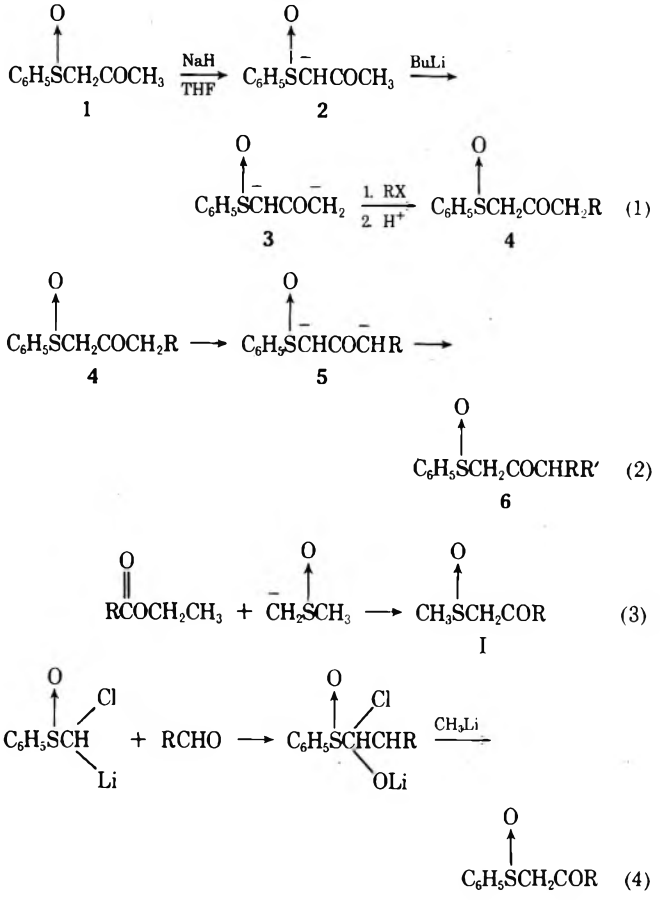
Received November 28, 1973

Alkylation of the Dianion of β-Keto Sulfoxides. A Versatile Synthesis of Phenyl (2-Oxoalkyl) Sulfoxides. A General Route to Ketones, 1,4 Diketones, and Aldols

Summary: General synthetic routes to phenyl (2-oxoalkyl) sulfoxides, ketones, 1,4 diketones, and aldols have been realized *via* dianions of β-keto sulfoxides.

Sir: We wish to report that dianion 3 derived from phenyl (2-oxopropyl) sulfoxide (1) can be generated and undergoes specific alkylation at the γ carbon atom (eq 1). In addition, dianions derived from γ-substituted β-keto alkyl sulfoxides undergo exclusive alkylation at the γ carbon (eq 2). The specific alkylation at γ carbon of 1 and 4 *via* dianions 3 and 5, respectively, makes phenyl (2-oxopropyl) sulfoxide (1) a useful reagent in organic synthesis (*vide infra*) and provides a general high yield synthesis of β-keto sulfoxides. Russell[1] and Corey[2] have previously shown that esters react with dimethyl sulfoxide anion to produce β-keto sulfoxides (eq 3). In addition, it had been reported[2] that compounds such as I could be reductively cleaved (aluminum amalgam) to yield methyl ketones. More recently it has been demonstrated that lithiated chloromethyl phenyl sulfoxide reacts with aldehydes affording an adduct which upon treatment with methyllith-

ium produced phenyl (2-oxoalkyl) sulfoxides (eq 4).[3] Procedures for the mono- and dialkylation at the α carbon of β-keto sulfoxides of type I have been reported;[4] however, no report describing the specific γ-alkylation of dianions derived from β-keto sulfoxides (*e.g.*, 3 and 5) has been reported.[5]



Treatment of phenyl (2-oxopropyl) sulfoxide[6] (1) with sodium hydride in anhydrous THF produced the soluble monoanion 2, and subsequent metalation of 2 with *n*-butyllithium generated dianion 3. When a solution of 3 in THF was treated with a variety of alkylating agents, including isopropyl iodide, a facile reaction occurred. The monoalkylated products were isolated in good yield (Table I). Yields have not been optimized.

Table I
Alkylation of Dianion from $C_6H_5S(\rightarrow O)CH_2COCH_3$

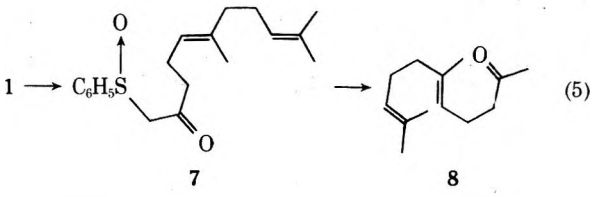
RX	Yield of 4,[a,b] %
$CH_3CH_2CH_2CH_2I$	78[c]
$(CH_3)_2CHI$	73[c]
$C_6H_5CH_2Cl$	63
$CH_2{=}CHCH_2Br$	65[c]
Geranyl bromide	61
m-Methoxybenzyl bromide	80

[a] All substances exhibited nmr, ir, and analytical data in accord with the assigned structures. [b] Crude yields were on the order of 80–90%. [c] Yield refers to crystalline material obtained by direct crystallization from crude product.

It was evident from the nmr spectra that alkylation occurred exclusively at the γ carbon. Spectral analysis of the crude reaction mixture failed to give any evidence of alkylation at the α carbon atom, dialkylation or O-alkylation. The nmr spectra of 4[7] have a two-proton singlet at δ 3.75 due to the α-methylene protons. The absence of a three-proton singlet at δ ~2.23 further indicated that alkylation occurred exclusively on the γ carbon.

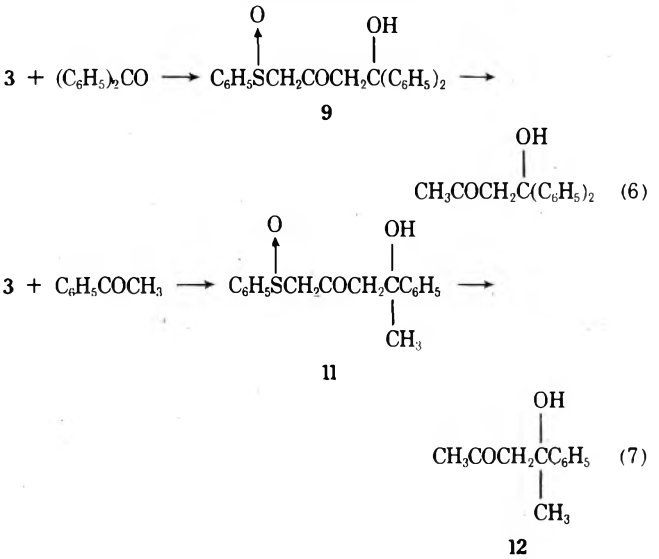
We have also alkylated γ-substituted β-keto sulfoxides. Treatment of phenyl (2-oxoheptyl) sulfoxide (4, R = *n*-Bu) with sodium hydride in THF followed by metalation with *n*-BuLi afforded dianion 5 (R = *n*-Bu) which upon addition of benzyl chloride resulted in a 72% isolated pure yield of 6 (R = *n*-Bu; R′ = benzyl). Similarly, allyl bromide, 1,3-dichloro-2-butene, and geranyl bromide underwent γ-alkylation.

Specific alkylation at the γ-carbon atom of 1 provides a general route to phenyl (2-oxoalkyl) sulfoxides which allows for an attractive synthetic route to a wide variety of methyl ketones[8] *via* reductive cleavage of the carbon–sulfur bond.[2] To demonstrate the efficiency of this ketone synthesis, we have carried out the synthesis of geranylacetone (8) (eq 5). Sulfoxide 1 (1 equiv, 1 *M* in THF) was

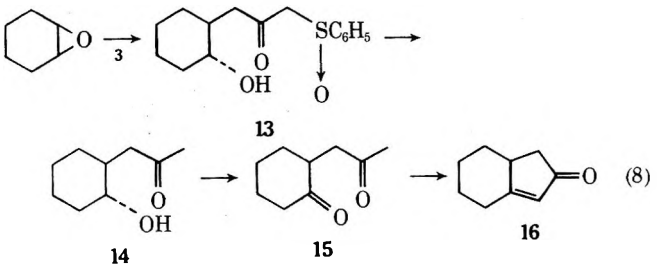


converted into monoanion 2 by treatment with a sodium hydride (1.1 equiv) in 1 ml of THF. After stirring at room temperature for 30 min, monoanion 2 was treated with *n*-butyllithium (1.1 equiv). After 20 min, geranyl bromide (1.1 equiv) was added. Stirring was continued for 10 min followed by the usual work-up. There was obtained after chromatography a 61% isolated yield of pure β-keto sulfoxide 7. Reductive cleavage of 7 with aluminum amalgam in 10% aqueous THF at 80° for ~1 hr afforded a 90% yield of geranylacetone (8) which was identical (nmr, ir, mass spectrum, glc) with an authentic sample.[9]

Dianions of β-keto sulfoxides undergo aldol reactions with carbonyl compounds. We have found that reaction of dianion 3 with benzophenone gave the aldol product 9 in 80% yield which upon treatment with Al/Hg afforded the aldol 10 in 90% yield (eq 6). Similarly, acetophenone reacted with dianion 3 affording adduct 11 in 77% yield which upon reductive cleavage afforded aldol 12 in 80% isolated pure yield (eq 7). The synthetic route outlined permits ready access to aldols (*e.g.*, 10 and 12) which are not readily available by alternate procedures.

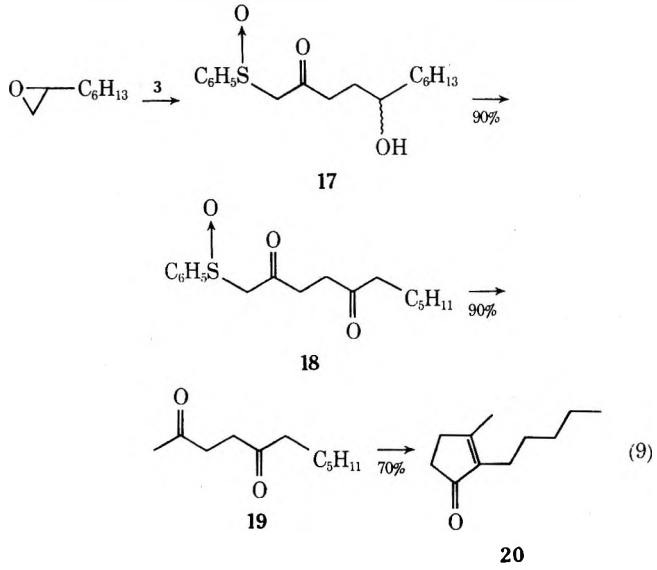


Finally, we wish to report that dianion 3 reacts with a variety of epoxides,[10] thus providing a convenient route to 1,4 diketones (eq 8). Treatment of cyclohexene oxide with



dianion **3** in THF at room temperature for 24 hr resulted in an 85% crude yield of ketol **13** (a 54% isolated yield of pure **13**, mp 104–105°, was obtained by direct crystallization of the crude product). Cleavage of the carbon–sulfur bond was achieved (Al/Hg) in aqueous THF as previously described in 85% yield. Jones oxidation of **14** followed by aldol condensation afforded hydrindenone **16** in 70% overall yield from **14**.

To further demonstrate the efficiency of this synthetic scheme, we have carried out the synthesis of dihydrojasmone[11] (**20**) as illustrated in eq 9. Reaction of the epoxide



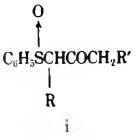
derived from 1-octene with dianion **3** in THF provided an 80% yield of ketol **17** (**17** was in equilibrium with its cyclic hemiacetal). Oxidation followed by reductive cleavage and cyclization afforded dihydrojasmone (**20**) which exhibited spectral properties in agreement with published data.[11]

This novel and efficient method for the construction of 1,4 diketones makes dianions of β-keto sulfoxides useful intermediates in organic synthesis. In addition, dianion **3** should provide an attractive synthetic route to a wide variety of ketones and aldols.[8]

Acknowledgment. We thank the National Cancer Institute (Public Health Service Research Grant No. RO1 CA 13689-02), Eli Lilly and Co., and the donors of the Petroleum Research Fund, administered by the American Chemical Society, for generous support of this research.

References and Notes

(1) G. A. Russell and H.-D. Becker, *J. Amer. Chem. Soc.*, **85**, 3406 (1963); H.-D. Becker, G. J. Mikol, and G. A. Russell, *ibid.*, **85**, 3410 (1963).
(2) E. J. Corey and M. Chaykovsky, *J. Amer. Chem. Soc.*, **87**, 1345 (1965).
(3) I. Kuwajima and Y. Fukuda, *Tetrahedron Lett.*, 327 (1973).
(4) P. G. Gassman and G. D. Richmond, *J. Org. Chem.*, **31**, 2355 (1966).
(5) We recently reported that dianions of β-keto phosphonates undergo specific alkylation on the γ carbon, providing a versatile synthesis of dimethyl (2-oxoalkyl) phosphonates [P. A. Grieco and C. S. Pogonowski, *J. Amer. Chem. Soc.*, **95**, 3071 (1973); P. A. Grieco and C. S. Pogonowski, *Synthesis*, 425 (1973)]. For a review on dianions of β-dicarbonyl compounds, see T. M. Harris and C. M. Harris, *Org. React.*, **17**, 155 (1969); L. Weiler, *J. Amer. Chem. Soc.*, **92**, 6702 (1970).
(6) Prepared by treatment of phenyl (2-oxopropyl) sulfide with sodium metaperiodate in aqueous methanol at 0° [C. R. Johnson and H. E. Keiser, *Org. Syn.*, **46**, 78 (1966)].
(7) The nmr spectrum of phenyl (2-oxopropyl) sulfoxide has the following signals: δ (CCl_4) 2.23 (s, 3 H, COMe), 3.80 (s, 2 H, $-CH_2-$), 7.55 (m, 5 H).
(8) One can prepare α- and γ-substituted β-keto sulfoxides (e.g., i) which provides for a general route to ketones (unpublished results, P. A. Grieco and C. S. Pogonowski).



(9) Kindly provided through the courtesy of Dr. Bernard J. Kane, Glidden-Durkee, Jacksonville, Fla.
(10) In addition to the epoxides cited, propylene oxide undergoes smooth reaction with dianion **3**. A report describing the opening of epoxides with the dianion of ethyl acetoacetate for the preparation of tetrahydrofurylidene acetates has recently appeared [T. A. Bryson, *J. Org. Chem.*, **38**, 3428 (1973)].
(11) H. C. Ho, T. L. Ho, and C. M. Wong, *Can. J. Chem.*, **50**, 2718 (1972), and references cited therein.

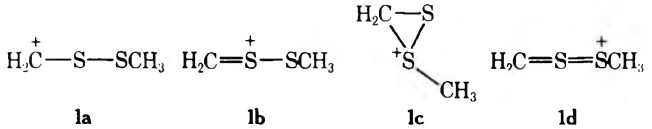
Department of Chemistry **Paul A. Grieco***
University of Pittsburgh **Chester S. Pogonowski**
Pittsburgh, Pennsylvania 15260

Received November 1, 1973

α-Disulfide Carbonium Ions

Summary: Evidence from solvolysis studies on chloromethyl methyl disulfide and spectroscopic studies with various disulfides is taken to indicate that acyclic α-disulfide carbonium ions are far less stable than α-sulfide carbonium ions.

Sir: While carbonium ion stabilization by adjacent thiyl groups is well-known,[1] the stability of α-disulfide carbonium ions has not been reported. In connection with studies involving α-heteroatom-substituted alkyl disulfides[2] we required information on the properties of the methyldithiomethyl cation (shown in various canonical or valence tautomeric representations **1a**–**1d**) and its alkyl-substituted derivatives. In this communication we present the preliminary results of our investigation.



We have determined the rate of hydrolysis of CH_3SSCH_2Cl[3] under S_N1 conditions, following the general procedure used by Bordwell in his classical study of the hydrolysis of α-chloro sulfides.[1a] The hydrolysis of a ~0.005 *M* solution of the α-chloro disulfide in 50% dioxane–water at 34.85° was followed using either an automatic titrator or a conductivity cell.[4] Least-squares analysis of data obtained from a duplicate run using a photometric titrator[5] automatically maintained at the pH 4.6 Bromphenol Blue end point gave a first-order rate constant of 1.82×10^{-4} sec^{-1} (correlation coefficient 0.995). A comparison of the rate constants for hydrolysis of CH_3SSCH_2Cl and CH_3SCH_2Cl (Table I) indicates a rate retardation for the former of over 6800, providing clear evidence for the decreased stability of $CH_3SSCH_2^+$ compared to $CH_3SCH_2^+$.

Table I
Rate Constants for the Hydrolysis of Chloromethyl Methyl Disulfide and Some Related Compounds at 34.85° in Aqueous Dioxane

Compd	$k \times 10^5$ sec^{-1}	Ref
p-$NO_2C_6H_4SCH_2Cl$	5.7	1a
CH_3SSCH_2Cl	18	This work
$(CH_3)_3CCl$	58	1a, this work
$C_6H_5SCH_2Cl$	560	1a
CH_3SCH_2Cl	123,000	8

Spectroscopic data on alkyl and vinyl disulfides and sulfides is also consistent with the lesser stability of α-disulfide carbonium ions compared to the corresponding α-thiyl carbonium ions. Thus, while the mass spectra of dialkyl sulfides show a prominent α-fission fragment (*i.e.*,

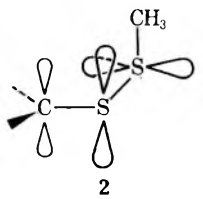
$$n\text{-}PrS\overset{\cdot+}{P}r\text{-}n \xrightarrow{-Et\cdot} n\text{-}PrSCH_2^+ \quad (1)$$

eq 1, 86% base),[6,7] this same process is insignificant in the mass spectra of dialkyl disulfides (*i.e.*, eq 2, 0.09% base).[6]

$$n\text{-}PrSS\overset{\cdot+}{P}r\text{-}n \xrightarrow{-Et\cdot} n\text{-}PrSSCH_2^+ \quad (2)$$

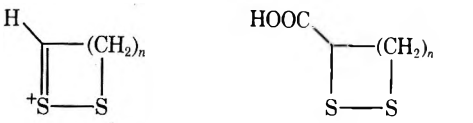
The extent of shielding of β-vinyl protons in the nmr spectra of vinyl compounds ($CH_2{=}CHX$, X = RS, R_2S^+, RO, R_2N, R_3Si) has been used as a measure of the importance of electron-donating resonance structures such as $^-CH_2{-}CH{=}X^+$ in competition with inductive and conjugative electron-withdrawing effects as in $^+CH_2{-}CH{=}X^-$.[9] The fact that β protons of vinyl disulfides are *less shielded* than β protons of vinyl sulfides supports the contention that the disulfide group is a poorer electron donor than the sulfide group (compare the chemical shifts of δ 4.84–4.97 and 5.08–5.11 for the β-vinyl protons, respectively, cis and trans to the alkylthio group in ethyl or methyl vinyl sulfide[9] with the corresponding *cis*- and *trans*-β-vinyl proton shifts of δ 5.40–5.45 and 5.25–5.30 in ethyl or methyl vinyl disulfide[10]) as indicated by a variety of chemical studies.[11]

To explain the low stability of **1** it can be argued that the near 90° C–S–S–C dihedral angle adopted by acyclic disulfides is also favored for ion **1**, thereby precluding any contributions from structure **1d** (since the requisite p orbitals are orthogonal as indicated in **2**). While **1c** could contribute to the overall stability of **1**, it could only do so at the expense of contributions from **1a** and **1b** (since the geometry favoring **1c** should differ from the ideal geometry for **1a** and **1b**).[12] The reduced stability of $CH_3SSCH_2^+$ compared to $CH_3SCH_2^+$ can be attributed to inductive and conjugative (*i.e.*, involving sulfur 3d orbitals) electron-withdrawal effects by the second sulfur atom.[13] From the data of Table I it is seen that, in electron-withdrawal ability, the CH_3S group is similar to the *p*-nitrophenyl group.

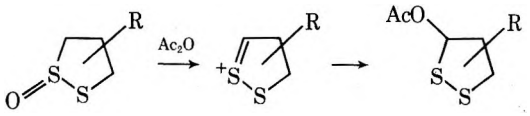


2

Cyclic disulfides display enhanced electron-donor properties (compared to acyclic disulfides) which increase with decreasing ring size and decreasing C–S–S–C dihedral angle.[11a,c] This phenomenon is explained in terms of the destabilization of the ground state of small ring disulfides due to lone pair–lone pair repulsion.[11] We suggest that the stability of cyclic α-disulfide carbonium ions (*i.e.*, **3**) should also increase with decreasing ring size since extended conjugation (as in **1b** and **1d**) should relieve lone pair repulsions. This postulate finds some support in the following observations: (1) the base peak in the mass spectrum of 1,2-dithiolane-3-carboxylic acid (**4a**) corresponds to ion **3a** while in the mass spectrum of 1,2-dithiane-3-carboxylic acid (**4b**) the peak corresponding to the M − CO_2H ion **3b** represents only 29% of the base intensity;[14] (2) 1,2-dithiolane *S*-oxide **5** undergoes a Pummerer rearrangement (presumably involving a carbonium ion such as **6** as a key intermediate) on treatment with acetic anhydride,[15] while, in our hands, *tert*-BuSS(O)Me[16] was unreactive under the same conditions.[17,18]



3a, $n = 2$ **4a**, $n = 2$
b, $n = 3$ **b**, $n = 3$



5 **6**

Finally, it should be noted that *α-alkylperoxy carbonium ions* (*i.e.*, $^+CH_2OOR$) should be less stable than α-alkoxy carbonium ions for essentially the same reasons advanced above to explain the relative instability of acyclic *α-disulfide carbonium ions*. Consistent with this argument is the observation that replacement of both alkoxy groups of an acetal with peroxy groups (*i.e.*, using *t*-BuOOH; see eq 3) requires more drastic conditions, such as acid catalysis, than replacement of a single alkoxy group (which occurs without catalyst).[20]

$$RCH(OEt)_2 + t\text{-}BuOOH \xrightarrow{\Delta} RCH(OEt)(OO\text{-}t\text{-}Bu) \xrightarrow[HClO_4]{t\text{-}BuOOH} RCH(OO\text{-}t\text{-}Bu)_2 \quad (3)$$

R = alkyl

Acknowledgment. It is a pleasure to thank Professors Stanley G. Smith and J. C. Martin for their generous assistance in this research while the author was a Visiting Professor at the University of Illinois—Urbana.

References and Notes

(1) (a) F. G. Bordwell, G. D. Cooper, and H. Morita, *J. Amer. Chem. Soc.*, **79**, 376 (1957); (b) H. Meerwein, K-F. Zenner, and R. Gipp, *Justus Liebigs Ann. Chem.*, **688**, 67 (1965); (c) R. A. Olofson and D. W. Hansen, Jr., *Tetrahedron*, **27**, 4209 (1971); (d) R. K. Hill and D. A. Cullison, *J. Amer. Chem. Soc.*, **95**, 2923 (1973).
(2) E. Block and J. O'Connor, *J. Amer. Chem. Soc.*, **95**, 5048 (1973).
(3) I. B. Douglass, J. V. Norton, R. L. Weichman, and R. B. Clarkson, *J. Org. Chem.*, **34**, 1803 (1969).
(4) On the basis of spectral and vpc analysis, the initial hydrolysis product from chloromethyl methyl disulfide appears to be hydroxymethyl methyl disulfide. The instability of this compound has thus far precluded isolation in pure form. Other α-hydroxy disulfides have been described as unstable substances [A. Binz, C. Rath and E. Walter, *Chem. Ber.*, **57B**, 1398 (1924)].
(5) Designed by R. Anderson and S. G. Smith; *cf.* S. G. Smith and D. J. W. Goon, *J. Org. Chem.*, **34**, 3127 (1969).
(6) American Petroleum Institute Research Project 44 Mass Spectra.
(7) S. Sample and C. Djerassi, *J. Amer. Chem. Soc.*, **88**, 1937 (1966).
(8) Estimated from the data of Böhme [H. Böhme, H. Fisher, and R. Frank, *Justus Liebigs Ann. Chem.*, **563**, 54 (1949)]; also see ref 1a.
(9) (a) M. C. Caserio, R. E. Pratt, and R. J. Holland, *J. Amer. Chem. Soc.*, **88**, 5747 (1966); (b) G. Ceccarelli and E. Chiellini, *Org. Mag. Resonance.*, **2**, 409 (1970).
(10) H. E. Wijers, H. Boelens, A. Van der Gen, and L. Brandsma, *Recl. Trav. Chim. Pays-Bas*, **88**, 519 (1969).

(11) (a) B. Lindberg and G. Bergson, *Ark. Kemi*, **23**, 319 (1965); (b) S. H. Smallcombe and M. C. Caserio, *J. Amer. Chem. Soc.*, **93**, 5826 (1971); (c) R. F. Hudson and F. Filippini, *J. Chem. Soc. Chem. Commun.*, 726 (1972); (d) T. C. Morrill, R. J. Opitz, and R. Mozzer, *Tetrahedron Lett.*, 3715 (1973); (e) S. Oae and M. Yoshihara, *Bull. Chem. Soc. Jap.*, **41**, 2082 (1968).
(12) For qualitative evidence for episulfonium ions from β-halo disulfides, see F. Lautenschlaeger and N. V. Schwartz, *J. Org. Chem.*, **34**, 3991 (1969), and N. M. Karimova, M. G. Lin'kova, O. V. Kil'disheva, and I. L. Knunyants, *Khim. Geterotsikl. Soedin.*, (1), 8 (1973) [*Chem. Abstr.*, **78**, 123970 (1973)].
(13) (a) A somewhat similar situation may prevail for $CH_3SSCH_2\cdot$ [*cf.* P. J. Krusic and J. K. Kochi, *J. Amer. Chem. Soc.*, **93**, 846 (1971)]; (b) for a dramatic demonstration of acceptive resonance by divalent sulfur, see C. B. Quinn and J. R. Wiseman, *ibid.*, **95**, 6120 (1973).
(14) J. H. Bowie, S.-O. Lawesson, J. O. Maden, C. Nolde, G. Schroll, and D. H. Williams, *J. Chem. Soc. B*, 946 (1966).
(15) I. Saito and S. Fukui, *J. Vitaminol. (Kyoto)*, **12**, 244 (1966).
(16) E. Block and S. W. Weidman, *J. Amer. Chem. Soc.*, **95**, 5046 (1973).
(17) An extreme example of a stabilized cyclic α-disulfide carbonium ion is the aromatic 1,2-dithiolium ion [*cf.* A. Hordvik, *Quart. Rep. Sulfur Chem.*, **5**, 21 (1970)].
(18) The C–S–S–C dihedral angle in dimethyl disulfide is actually somewhat less than 90° (~85° in the gas phase[19]) and a similar situation may prevail for CH_3SSCH_2Cl and ion **1**. Preliminary kinetic measurements on the rate of hydrolysis of $(CH_3)_3CSSCH_2Cl$, a compound which on steric grounds[19] might be expected to have a dihedral angle closer to 90°, indicate a rate constant less than half as large as that for CH_3SSCH_2Cl. This result, which is in the opposite direction from that expected on the basis of inductive effects, is consistent with the dihedral angle arguments presented above.
(19) H. Bock and G. Wagner, *Angew. Chem., Int. Ed. Engl.*, **11**, 150 (1972).
(20) A. Rieche and C. Bischoff, *Chem. Ber.*, **94**, 2457 (1961); A. Rieche, C. Bischoff, and P. Dietrich, *ibid.*, **94**, 2932 (1961). I thank Dr. José Pazos for bringing these parallels to disulfide chemistry to my attention.
(21) Visiting Professor at Harvard University, 1974. Address correspondence to author at the Department of Chemistry, Harvard University, Cambridge, Mass. 02138.

Department of Chemistry **Eric Block**[21]
University of Missouri—St. Louis
St. Louis, Missouri 63121

Received December 12, 1973

The Chlorination of Cyclopentadiene

Summary: Chlorination of cyclopentadiene under ionic condition in several solvents produces (in varying amounts) the following dichlorides (yields ~60%): *cis*-3,4-dichlorocyclopentene (**1**), *trans*-3,4-dichlorocyclopentene (**2**), *cis*-3,5-dichlorocyclopentene (**3**), and *trans*-3,5-dichlorocyclopentene (**4**); **1** is formed by cis-1,2 addition of chlorine.

Sir: We wish to report the first example of extensive *cis*-1,2 addition of chlorine to a simple, aliphatic olefinic system.[1] The results in Table I show that chlorination of cyclopentadiene gives *cis*-3,4-dichlorocyclopentene (**1**) under all of the conditions that were examined.

Table I
Chlorination of Cyclopentadiene

Solvent	Percentage of dichlorides 1	2	3	4	Yield, %
CH_2Cl_2	38	35	18	9	52
CCl_4	27	23	39	11	60
C_5H_{12}	13	29	29	28	68

The stereochemistry of 1,2 addition of chlorine to cyclopentadiene stands in marked contrast to cyclopentene. We have established that chlorination of cyclopentene does not give a trace of the cis-1,2 isomer.[2] We account for the difference in the stereochemistry of 1,2 addition between these two olefins on the basis of the bonding between the chlorine and carbon atoms in intermediates **5** and **6**.

5 **6**

Intermediate **5** (from cyclopentene) gives only trans addition, apparently because bonding between the carbon atoms and chlorine atoms prevents cis attack of the chloride ion. By contrast, intermediate **6** (from cyclopentadiene) has no bonding (or weak, in the case of pentane) between the chlorine atom and adjacent allylic carbon atom, and the chloride ion can attack either cis or trans to the chlorine atom. The results in Table I also suggest that the charge density in intermediate **6** in the least polar solvent pentane is highly dispersed since considerable attack occurs at both ends of the allylic system (ratio of 1,2:1,4 addition equals 1:1.3). In polar dichloromethane the charge density is substantially localized at one allylic carbon atom (ratio of 1,2:1,4 addition equals 1:0.3).

Our results are in sharp disagreement with rather recent studies on the chlorination of cyclopentadiene. One study[3] states that the only product is **4**, and the other investigators claim[4] that 3,5-dichlorocyclopentene (85%) is the principal product (3,4-dichlorocyclopentene, 15%); the stereochemistry was not established.[5]

Reactions were carried out (−15°) at 0.02 mol fraction in diene in the selected solvent (reaction volume ~25 ml) in the presence of O_2. The chlorine was added both as a gas and dissolved in solvent, without any significant differences. Under these conditions cyclohexane was not chlorinated, which confirmed ionic conditions. (Under radical conditions cyclohexane was chlorinated.) Vpc and nmr analyses of reaction mixtures were in close agreement indicating that there was no rearrangement during vpc analysis. Although the yields are not quantitative, the product compositions in Table I seem to be valid since chlorinations at both very low and high completion gave essentially the same mixtures of dichlorides.

Vpc analysis (2.5% SE-30, 18 ft × 0.25 in., 55°, and 100 ml/min) of chlorination mixtures showed four principal peaks with retention times of 9.2, 11.0, 15.4, and 16.4 min. The peaks were assigned to **2**, **4**, **3**, and **1**, respectively. Pure samples of **2** and **4** were isolated from chlorination mixtures by distillation or vpc collection; **1** and **3** were obtained together as a mixture. Samples of **3** and **4** were obtained by independent synthesis from their corresponding dibromides as follows: *cis*- or *trans*-3,5-dibromocyclopentene was allowed to react with excess lithium chloride in DMSO at 15° for 15 min, after which the mixture was added to water and the product extracted into pentane. Structural assignments for **2**, **3**, and **4** are therefore based on independent synthesis (**3** and **4**) and their nmr spectra. The nmr spectra of **2**, **3**, and **4** are strikingly similar to the spectra of the corresponding cyclopentadiene dibromides.[6] The 60-MHz spectral data (CCl_4) for the four dichlorides is summarized as follows. **1**: δ 2.71 (br d, 2, CH_2, $J_{5(5')4}$ = 7.0 Hz), 4.45 (dt, 1, CH_2CHCl, $J_{45(5')}$ = 7.0, J_{43} = 5.7 Hz), 4.89 (d, 1, CH=CHCHCl, J_{34} = 5.7 Hz), 5.99 (br s, 2, CH=CH). **2**: 2.52 [br d, 1, *cis*-C(Cl)C(**H**)H, $J_{55'}$ = 18.2 Hz], 3.15 [dd, 1, *trans*-C(Cl)C(**H**)H, $J_{5'5}$ = 18.2, $J_{5'4}$ = 6.0 Hz], 4.48 [d, 1, CH_2C(**H**)Cl, $J_{45'}$ = 6.0 Hz], 4.91 [br s, 1, CH=CHC(**H**)Cl], 5.88 (br s, 2, CH=CH). **3**: 2.30 [dd, 1, *cis*-C(Cl)C(**H**)H, $J_{44'}$ = 15.7, $J_{43(5)}$ = 3.0 Hz], 3.06 [dd, 1, *trans*-C(Cl)C(**H**)H, $J_{4'4}$ = 15.7, $J_{4'3(5)}$ = 7.4 Hz], 4.89 (dd, 2, CHCl, J = 3.0, J = 7.4 Hz), 5.95 (d, 2, CH=CH, J = 1.0 Hz). **4**: 2.66 (t, 2, CH_2, J = 5.4 Hz), 5.17 (t, 2, CHCl, J = 5.4, J = 1.1 Hz), 6.06 (d, 2, CH=CH, J = 1.1 Hz).

Assignment of structure **1** to vpc peak no. 4 was made on the basis of the following evidence (a) the ir spectrum of **1** (mixed with **3**) showed no absorptions inconsistent with the proposed structure; (b) when **1** (mixed with 35% **3**) was heated in a sealed tube for 4 days (temp 100°), it largely rearranged to a mixture of **2**, **3**, and **4** (we confirmed that significant net loss of isomers did not occur by including *p*-chlorobromobenzene in the mixture as an internal standard); and (c) the nmr spectrum is consistent with this structure. As stated above, the spectrum showed four regions of absorptions (60 MHz, δ 2.71, 4.45, 4.89, 5.99) with integrated intensities of 2:1:1:2, respectively. Decoupling experiments (Varian XL-100) showed that the multiplet at δ 4.45 collapsed to a doublet when the protons centered at 2.71 were irradiated. Irradiation of the proton centered at δ 4.89 caused the multiplet at 4.45 to collapse to a triplet. The broad doublet at δ 2.71 collapsed to a broad singlet when the proton at 4.45 was irradiated. Unlike the trans-3,4 isomer, **2**, the methylene hydrogens in **1** apparently have the same chemical shift and do not couple with each other.

Acknowledgment. Support for this work was provided by the Research Corporation, the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the Union Oil Co. of California Foundation, Brea, Calif. The authors wish to express appreciation for the use of nmr facilities to the Departments of Chemistry of Southwestern State College, Weatherford, Okla., and the University of Oklahoma, Norman, Okla.

Reference and Notes

(1) Cis-1,2 addition of chlorine has been observed with phenanthrene [P. B. D. de la Mare, N. V. Klassen, and R. Koenigsberger, *J. Chem. Soc.*, 5285 (1961)] and acenaphthalene [S. J. Cristol, F. R. Stermitz, and P. S. Ramey, *J. Amer. Chem. Soc.*, **78**, 4939 (1956)] and has been suspected in the cases of 1-phenylpropene [R. C. Fahey and C. Schubert, *ibid.*, **87**, 5172 (1965)] and stilbene [S. J. Cristol and R. S. Bly, *ibid.*, **82**, 142 (1960)]. In these four olefins the double bond is in conjugation with an aromatic ring.
(2) cis-1,2-Dichlorocyclopentane was synthesized according to the procedure that N. Isaacs and D. Kirkpatrick [Tetrahedron Lett., 3869 (1972)] used for the preparation of cis-1,2-chlorocyclohexane.
(3) F. Tailly, *Bull. Soc. Chem. Fr.*, 38 (1962).
(4) K. Heinz Buechel, A. Ginsberg, and R. Fischer, *Chem. Ber.*, 99 (2), 421 (1966).
(5) It is conceivable that the structural assignments in the previous studies[3,4] were correct, but that the assignments were made on thermodynamic rather than kinetic products. We have found that the thermodynamic dichloride mixture (formed by heating a dichloride mixture) consists of predominately 3,5-dichlorides. In the previous studies the dichloride products were distilled without regard for rearrangement.
(6) A detailed analysis of the nmr spectra of the dibromides corresponding to dichlorides **2**, **3**, and **4** has recently been published in this journal [G. E. Heasley, V. L. Heasley, S. L. Manatt, H. A. Day, R. V. Hodges, P. A. Kroon, D. A. Redfield, T. L. Rold, and D. E. Williamson, *J. Org. Chem.*, **38**, 4109 (1973)].

Department of Chemistry
Point Loma College
(formerly Pasadena College)
San Diego, California 92106

Victor L. Heasley*
Paul D. Davis
D. Michael Ingle
Kerry D. Rold

Department of Chemistry
Bethany Nazarene College
Bethany, Oklahoma 73008

Gene E. Heasley

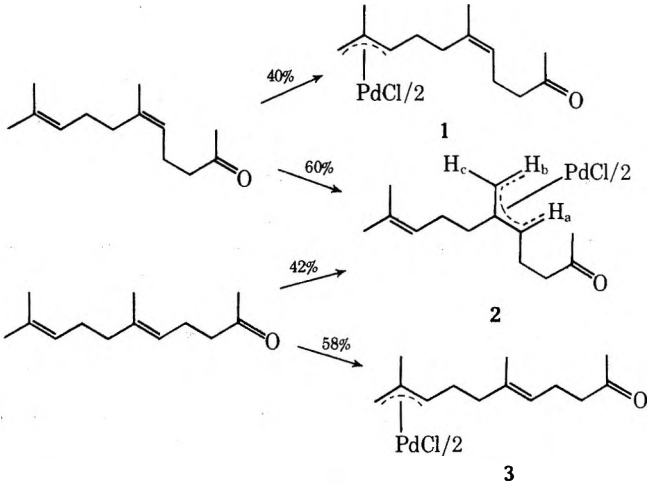
Received October 23, 1973

New Synthetic Reactions. Chemospecificity of Allylic Alkylation

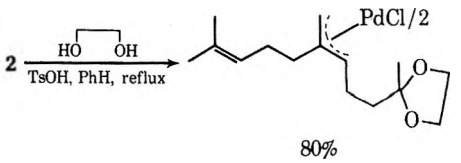
Summary: Selective alkylation of the methyl groups of geranylacetone without protection of the carbonyl group has been aschieved *via* the intermediacy of π-allylpalladium complexes.

Sir: The activation of the α position of carbonyl compounds for formation of carbon–carbon bonds contributes to the importance of the carbonyl group in organic synthesis. The double bond has not generally served such a role.[1] One approach to this problem involves alkylations utilizing π-allylpalladium complexes as intermediates which, in turn, are generated from the olefins.[2] We wish to report that this method allows selective alkylation α to the double bond even in the presence of a carbonyl group.

Treatment of *cis*- or *trans*-geranylacetone with palladium chloride, sodium chloride, cupric chloride, and sodium acetate in acetic acid proceeds regiospecifically to produce the π-allylpalladium chloride dimers **1** and **2** (from cis) and **2** and **3** (from trans) in 70–85% yields.[3,4] The isomers are easily separated by preparative tlc and characterized by their nmr spectra. Isomers **1** and **3** are distinguished from **2** by the presence of the methyl group on the π-allyl unit at δ 2.12 and 2.10, respectively.[5] They are distinguished from each other by the downfield chemical shift of the vinyl methyl group of **1** (δ 1.70) compared to **3** (1.65).[6] It should be noted that the geometry of the double bond of these products completely reflects that of starting material. However, reaction at the central double bond leads to the same π-allylpalladium chloride dimer from either *cis*- or *trans*-geranylacetone.[3] The syn stereochemistry of **2** is assigned on the basis of comparing nmr spectral characteristics (δ_{Ha} 3.40, δ_{Hb} 2.70, and δ_{Hc} 3.63) to related complexes of known stereochemistry.[3,5] Recovered geranylacetone from these preparations shows no loss of double-bond geometry.



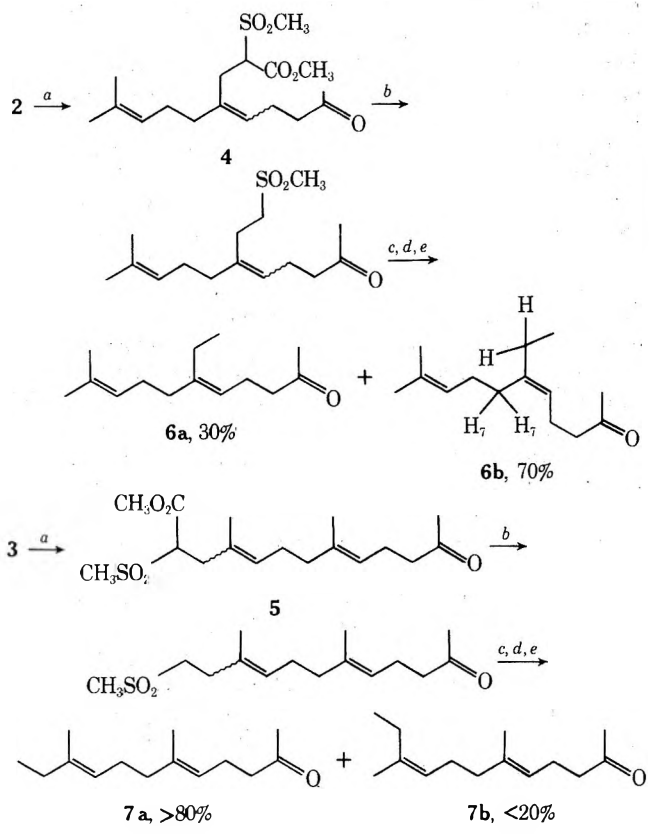
The remarkably stability of these complexes is illustrated by the ability to ketalize the carbonyl group without decomposition under normal conditions. On the other hand, such protection was unnecessary for subsequent alkylation. Treatment of either **2** or **3** with the anion of



80%

methyl methylsulfonylacetate in the presence of 4 equiv of triphenylphosphine leads to the allylic alkylation products **4** and **5**, respectively, in yields of 24–85% (see Scheme I). To prove the stereochemistry of the newly created double bond, **4** and **5** were converted to the olefins **6** and **7**, a net homologation of the methyl groups of geranylacetone. Lithium iodide in the presence of sodium cyanide effected decarbomethoxylation in 77–78%.[7] Reductive desulfurization was achieved after protecting the carbonyl group in an overall yield of 47–67%.[8] Vpc and nmr characteristics

Scheme I
Alkylation of π-Allylpalladium Complexes



[a] NaH, $CH_3SO_2CH_2CO_2CH_3$, THF, 25°. [b] LiI·$3H_2O$, NaCN, DMF, 130°. [c] $HOCH_2CH_2OH$, PhH, TsOH, reflux. [d] Li, $C_2H_5NH_2$, 0°. [e] H_2O, HCl.

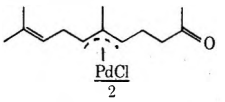
allowed the assignment of **6b** and **7a** as the major isomers. It has been shown that, in this series of compounds, cis isomers have shorter vpc retention times than trans.[6] The retention times for **6a** and **6b** are 14.4 and 13.6 min, respectively. Compounds **6b** shows a greater europium(+3) induced shift of the methylene group at C-7 than the methylene protons of the ethyl group. This observation implies a closer proximal relationship of the former methylene group to the carbonyl group. Finally, **7a** shows a single absorption in the nmr spectrum for both olefinic methyl groups, whereas **7b** is known to show two peaks for these groups.[9] As indicated before, the chemical shifts of methyl groups on trisubstituted double bonds has been shown to be diagnostic of olefin geometry.[6]

This study demonstrates the high regiospecificity of both the complex formation and alkylation. Furthermore, the stereochemistry of the newly formed double bond mainly reflects the stereochemistry of the π-allyl complex. More significantly, the method allows selective alkylation at the allylic site without the need to protect the carbonyl. The ability to create more complex structures with moderate stereospecificity and high chemospecificity from simple olefins should prove to be a useful addition to the arsenal of synthetic reactions.

Acknowledgment. We wish to thank the National Institutes of Health and the National Science Foundation for their generous support of our programs. We are indebted to Professor William G. Dauben for a generous gift of pure *cis*-and pure *trans*-geranylacetone.

References and Notes

(1) For use of olefin metalations in organic synthesis, see R. J. Crawford, W. F. Erman, and C. D. Broaddus, *J. Amer. Chem. Soc.*, **94**, 4298 (1972); R. J. Crawford, *J. Org. Chem.*, 37, 3543 (1972); J. Klein and A. Medlik, *Chem. Commun.*, 275 (1973); M. Schlosser and J. Hartmann, *Angew. Chem.*, **85**, 544 (1973); G. L. Hodgson, D. F. MacSweeney, and T. Money, *Chem. Commun.*, 236 (1973).
(2) B. M. Trost and T. J. Fullerton, *J. Amer. Chem. Soc.*, **95**, 292 (1973).
(3) For related work, see R. Hüttel and M. McNiff, *Chem. Ber.*, **106**, 1789 (1973); H. C. Volger, *Recl. Trav. Chim. Pays-Bas*, **88**, 225 (1969); A. D. Ketley and J. Braatz, *Chem. Commun.*, 169 (1968); W. H. Urry, private communication.
(4) In early runs without cupric chloride, an 85% yield of a mixture of **2** and **i** was obtained with only trace amounts of **1** or **3**. However, **i** has not been found in later preparations.



i

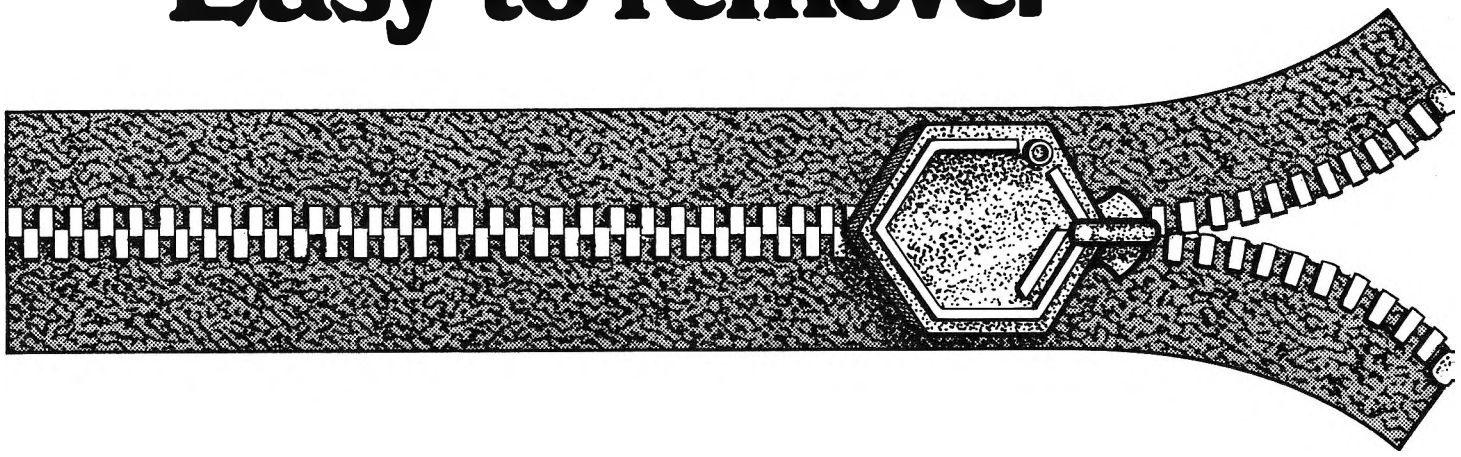
(5) K. Vrieze, A. P. Praat, and P. Cossee, *J. Organometal. Chem.*, **12**, 533 (1968); P. W. N. M. Van Leeuwen, J. Lukas, A. P. Praat, and M. Appleman, *ibid.*, **38**, 199 (1972); K. Vrieze, C. Maclean, P. Cossee, and C. W. Hilbers, *Recl. Trav. Chim. Pays-Bas*, **85**, 1077 (1966).
(6) (a) B. M. Trost, *Accounts Chem. Res.*, **3**, 120 (1970). (b) A 15 ft × 0.25 in. 20% SE-30 on Chromosorb W was employed for this analysis.
(7) *Cf.* J. E. McMurry and G. B. Wong, *Syn. Commun.*, **2**, 389 (1972); P. D. G. Dean, *J. Chem. Soc.*, 6655 (1965); F. Elsinger, J. Schreiber, and A. Eschenmoser, *Helv. Chim. Acta*, **43**, 113 (1960).
(8) W. E. Truce, D. P. Tate, and D. N. Burdge, *J. Amer. Chem. Soc.*, **82**, 2872 (1960); W. E. Truce and J. J. Breiter, *ibid.*, **84**, 1621, 1623 (1962).
(9) K. Mori, B. Stalla-Bourdillon, M. Ohki, M. Matsui, and W. S. Bowers, *Tetrahedron*, **25**, 1667 (1969).
(10) Camille and Henry Dreyfus Teacher-Scholar Grant Recipient.

Department of Chemistry
University of Wisconsin
Madison, Wisconsin 53706

Barry M. Trost*[10]
Thomas J. Dietsche
Terry J. Fullerton

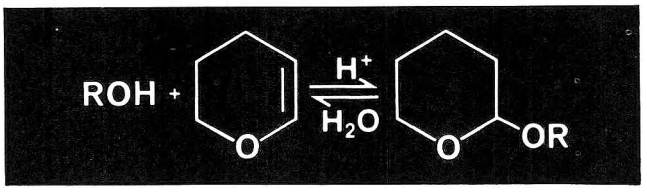
Received October 9, 1973

Easy to put on. Easy to remove.



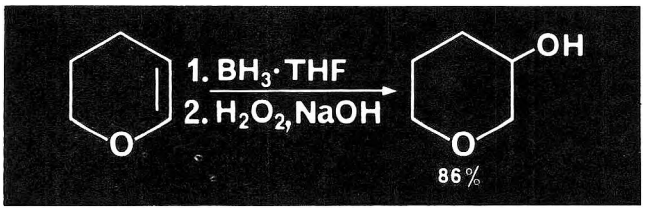
2,3-DIHYDROPYRAN from Aldrich protects alcohols, opens the way to many new compounds.

Tetrahydropyranyl ethers, readily formed from the reaction of 2,3-dihydropyran with alcohols under mild catalysis,[1,2] are very useful protecting groups for alcohols because they are stable to base, Grignard reagents, $LiAlH_4$, acetic anhydride and Jones oxidizing agent,[2] yet are rapidly cleaved by dilute acid.



2,3-Dihydropyran has also been used to protect carboxyl groups,[2] sulfhydryl groups,[2] propargylic alcohols,[2] the imidazole nitrogen of purines[2] and the 2′-hydroxyl of 5′-nucleotide monomers.[3] Typical applications include the total syntheses of prostaglandins[4] and humulene.[5]

The activated double bond of 2,3-dihydropyran also reacts with halogens, hydrogen halides, ketenes, and amides.[2] Hydroboration of 2,3-dihydropyran, followed by oxidation, affords 3-hydroxytetrahydropyran in 86% yield.[6]



In addition, 2,3-dihydropyran reacts with carboxylic acids to form polymers.[7] It has also been employed in the preparation of lysine[8] and 5-hydroxyvaleraldehyde.[9]

Thus, 2,3-dihydropyran is potentially very useful both as a protecting agent and as a starting material for a wide variety of compounds.

References

1) H. Alper and L. Dinkes, *Synthesis*, 81 (1972).
2) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Vol. I, John Wiley and Sons, Inc., New York, N.Y., 1967, p 256.
3) D. B. Straus and J. R. Fresco, *J. Amer. Chem. Soc.*, **87**, 1364 (1965).
4) E. J. Corey, H. Shirahama, H. Yamamoto, S. Terashima, A. Venkateswarlu and T. A. Schaaf, *ibid.*, **93**, 1490 (1970).
5) E. J. Corey and E. Hamanaka, *ibid.*, **89**, 2758 (1967).
6) G. Zweifel and J. Plamondon, *J. Org. Chem.*, **33**, 898 (1970).
7) Fr. Patent 1,551,932, *Chem. Abstr.*, **71**, 40399j (1969).
8) A. O. Rogers, R. D. Emmick, L. W. Tyran, L. B. Phillips, A. A. Levine and N. D. Scott, *J. Amer. Chem. Soc.*, **71**, 1837 (1949).
9) L. E. Schniepp and H. H. Geller, *ibid.*, **68**, 1646 (1946).

Catalog prices: **D10,620-8 2,3-Dihydropyran**

100g $6.50 **100kg $18.00/kg**
500g $24.00 **1000kg $12.00/kg**
Ton quantities available from stock

Aldrich

Aldrich Chemical Company, Inc.

Home Office:
Aldrich Chemical Co., Inc.
940 W. St. Paul Ave.
Milwaukee, Wisconsin 53233

In Great Britain:
Ralph N. Emanuel Ltd.
264 Water Rd., Wembley, Middx.
HAO 1PY, England

In Continental Europe:
Aldrich-Europe
B-2340 Beerse
Belgium

In Germany:
EGA-Chemie KG
7924 Steinheim am Albuch
Germany

CIRCLE 807 ON READER SERVICE CARD